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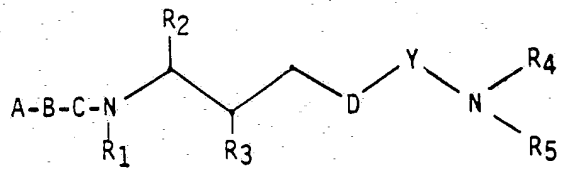
EP 0163237 EP 0152255 EP 0081783
DE 3601248
Hypertension 8 (6, PE2)II-1 to II-5 (1986)Pept. Struct. Funct. Proc Am. Pept. Sym. 8th ed. by V.J. Hruby and D.H. Rich (1983)p.511-20. Tetra hedron letters 24 (41) 440-4 (1983)

(58) Field of search
C2C
C3H

(54) Resin Inhibitators

(57) A compound of formula



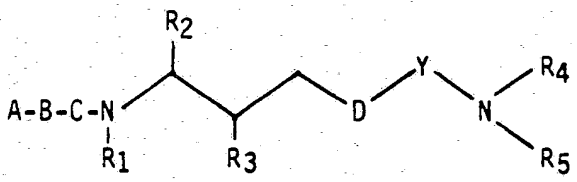
where
A is an acyl group;
B and C are bonds or represent amino-acids with at least one amino-acid being present;
R_2 is a side chain of an amino-acid;
R_3 is H, OH, acyloxy or NH_2;
D is a bond, O, >N R_1, or> CH-R_1;
Y is >CO, >SO_2 or >P(O) NR_4 R_5;
R_1 is H or alkyl;
and NR_4 R_5 is an amino function,
These compounds have renin-inhibiting activity and are for use against hypertension and cardiac insufficiency.

GB 2 200 115 A

Case 100-7005

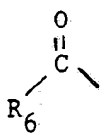
NOVEL PEPTIDE DERIVATIVES, THEIR PRODUCTION AND USE

The present invention relates to novel Renin-inhibitors, their preparation, use and pharmaceutical compositions containing them. The invention provides a compound of Formula I



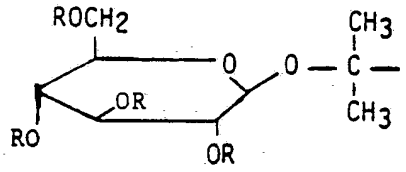
I

wherein

A signifies an acyl group of formula  wherein

R_6 denotes straight-chain or branched (C_{1-10})alkyl radical which may be optionally substituted by (C_{1-5})alkoxy or ($C_{6-}C_{10}$)aryloxy; a (C_{3-7})cycloalkyl radical, a (C_{3-10})-cycloalkyl-(C_{1-5})alkyl radical, a (C_{6-10})aryl radical, a 5- or

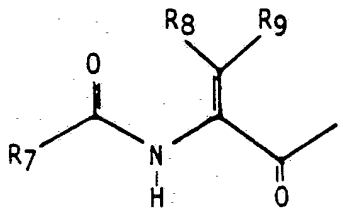
6-membered heteroaryl radical containing one or two nitrogen atoms, oxygen or sulphur atoms or one nitrogen atom and one oxygen atom and/or one sulphur atom; or a heteroaryl-(C_{1-5})-alkyl radical wherein the heteroaryl moiety is 5- or 6-membered and contains one or two nitrogen atoms, oxygen or sulphur atoms or one nitrogen atom and one oxygen atom and/or one sulphur atom; a straight-chain or branched (C_{1-5})alkoxy radical or a (C_{6-10})aryl-(C_{1-5})-alkoxy radical or a group of formula $R_{10}O(CH_2CH_2O)_n(CH_2)_m-$, wherein R_{10} signifies a straight-chain or branched (C_{1-5})alkyl radical, n signifies a whole number from 1 to 20 and m signifies a whole number from 1 to 5, or a group of Formula



wherein

R signifies hydrogen or acetyl
or

A signifies a group of formula



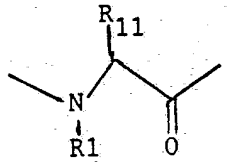
wherein

R_7 signifies a straight-chain or branched (C_{1-5})alkyl radical or a (C_{6-10})aryl radical and

R_8 and R_9 respectively denote hydrogen, a straight-chain or branched (C_{1-5})-alkyl radical or a (C_{6-10})aryl radical,

R_1 signifies hydrogen or a straight-chain or branched (C_{1-5})-alkyl radical,

B and C are the same or different and signify a bond or a group of formula



wherein

R_1 is defined as above and R_{11} signifies a hydrophilic or lipophilic amino acid side chain,

whereby

B and C cannot simultaneously signify a bond

D signifies a bond or denotes -O-, $-\underset{\displaystyle R_1}{\overset{|}{N}}-$ or $-\underset{\displaystyle R_1}{\overset{|}{CH}}-$

whereby R_1 is defined as mentioned above,

R_2 denotes a straight-chain or branched (C_{1-10})alkyl radical, a (C_{3-10})cycloalkyl(C_{1-5})alkyl radical which is optionally substituted in the cycloalkyl moiety, a (C_{6-10})aryl-(C_{1-5})-alkyl radical or a heteroaryl-(C1-5)-alkyl radical, wherein the heteroaryl moiety is 5- or 6-membered and contains one or two nitrogen atoms, oxygen or sulphur atoms or one nitrogen

atom and one oxygen atom and/or one sulphur atom, or a group of formula

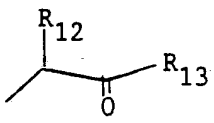
$$R_{15}-\overset{(O)_s}{\overset{\|}{S}}-(CH_2)p\ -$$

wherein

R_{15} signifies Hydrogen, (C_{1-4})alkyl or benzyl, s is 0 or 1 and p is 1 or 2,

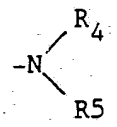
R_3 signifies hydrogen, a hydroxyl group, an amino group or a group of formula $-OCOR_2$, wherein R_2 is defined as above,

R_4 and R_5 are the same or different and respectively signify hydrogen, a straight-chain or branched (C_{1-5})alkyl radical, a (C_{6-10})-aryl-(C_{1-5})-alkyl or a heteroaryl-(C1-5)-alkyl radical, wherein the heteroaryl moiety is 5- or 6-membered and contains one or two nitrogen atoms, oxygen or sulphur atoms or one nitrogen atom and one oxygen atom and/or one sulphur atom,

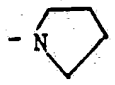
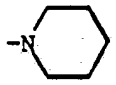
or it denotes a group of formula 

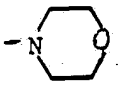
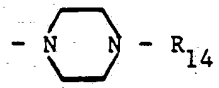
wherein R_{12} signifies a straight-chain or branched (C_{1-5})-alkyl radical or a straight-chain or branched (C_{1-5})-hydroxy-alkyl radical, R_{13} denotes a hydroxyl radical, a straight-chain or branched (C_{1-5})alkoxy group, an amino group or a (C_{1-5})alkylamino group, whereby the alkyl radical is straight-chain or branched, an aminomethylpyridyl group

or a benzyl group, or

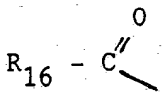
the radical 

denotes groups of formulae

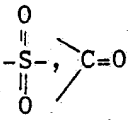
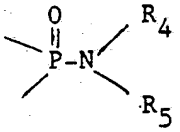
 , 

 or 

wherein R_{14} signifies hydrogen, (C_{1-5})-alkyl, benzyl, or a group of formula



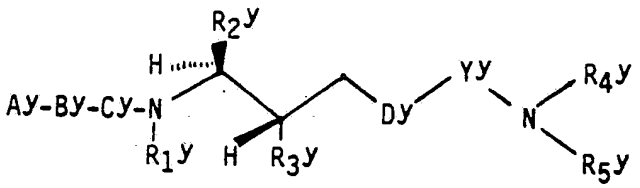
wherein R_{16} denotes (C_{1-4})Alkyl or (C_{1-4})alkoxy $(OC_2H_2)q-CH_2-$ wherein q signifies a whole number from 2 to 5.

Y signifies  or 

wherein R_4 and R_5 have the significances given above.

The C-atoms which are substituted by R_2 and R_3 may have R- or S-configuration. Compounds of formula I, wherein the C-atoms which are substituted by R_2 and R_3 have the configuration given in formula Iy, are preferred.

Preferred compounds of formula I possess the formula Iy



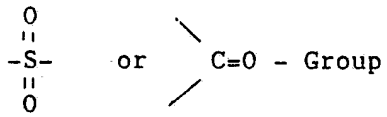
Iy

wherein

A^y signifies tert.-butyloxycarbonyl, pivaloyl, bis(1-naphthylmethyl)acetyl, benzoyl or 1-adamantylcarbonyl,

B^y signifies a bond, phenylalanine or β-cyclohexylalanine,

C^y signifies histidine, norleucine, phenylalanine or leucine,

Y^y signifies a  or C=O - Group

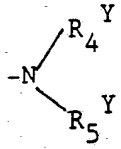
R_1^y signifies hydrogen or methyl,

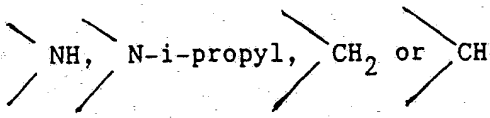
R_2^y signifies isobutyl, benzyl, cyclohexylmethyl or 1-adamantylmethyl,

R_3^y signifies hydroxy, amino or groups of formulae $OCOCH_3$ or $OCOC(CH_3)_3$,

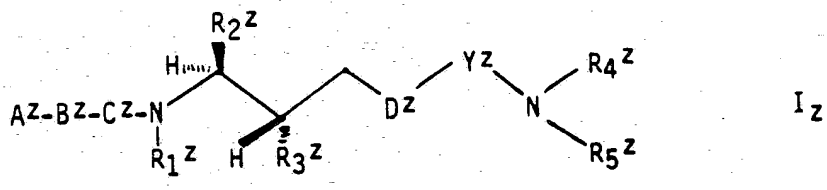
R_4^y signifies hydrogen, methyl, i-propyl, i-butyl or n-butyl,

R_5^y signifies methyl, i-propyl, i-butyl or n-butyl, or

the group  signifies a pyrrolidinyl-, piperidinyl or a morpholinyl-group and

D^y signifies  NH, N-i-propyl, CH_2 or CH-i-propyl-groups.

Especially preferred compounds of formula I possess formula I_z



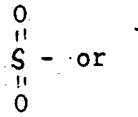
I_z

wherein

A^z signifies tert.-butyloxycarbonyl or bis(1-naphthylmethyl)-acetyl,

B^z signifies a bond, phenylalaninyl or β-cyclohexylalaninyl,

C^z signifies histidine, leucine or norleucine,

Y^z signifies a  - or a  C = O-group

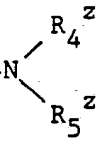
R_1^z signifies hydrogen,

R_2^z signifies cyclohexylmethyl or 1-adamantylmethyl,

R_3^z signifies hydroxy or amino,

R_4^z signifies hydrogen or methyl,

R_5^z signifies hydrogen, isopropyl or isobutyl or

The group  signifies a pyrrolidinyl-, a piperidinyl or a morpholinyl-group and

D^z signifies  NH- or  CH-isopropyl- or  CH_2-groups.

In formulae I, R_6 when it is a straight-chain or branched alkyl with 1 to 10 carbon atoms it signifies in particular methyl, ethyl, propyl, isopropyl, butyl, tert. butyl, 2,2-dimethylethyl, pentyl, hexyl etc., especially methyl, tert.-butyl and 2,2-dimethylethyl, and when it is substituted by aryloxy, it signifies specially phenoxymethyl or 1- or 2-naphthyloxymethyl, preferably 1-naphthyloxymethyl, when it is cycloalkyl with 3-7 carbon atoms, it signifies cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, when it is (C_{3-10})cycloalkyl-(C_{1-5})alkyl, cycloalkyl may have the significances given above, and may additionally signify adamantyl, and is especially cyclohexylethyl or (1-adamantyl)ethyl, when it is (C_{6-10})aryl, it signifies especially phenyl or 1- or 2-naphthyl, preferably 1-naphthyl, when it is a heteroaryl radical, it signifies in particular pyridyl, thienyl or furyl, when it is a heteroarylalkylradical the heteroaryl moiety and the alkyl moiety preferably have the above-mentioned signififcances, when it is a straight-chain or branched alkoxy radical, it especially signifies ethoxy or tert. butoxy, and when it is (C_{6-10})aryl-(C_{1-5})-alkoxy, it has in particular the significances given above for aryl and alkyl, and is preferably benzyloxy.

Then denotes A the corresponding carbonyl compounds of R_6.

R_7 when it is (C_{1-5})alkyl has the significances given above for alkyl, and when it is aryl, it signifies in particular phenyl or 1- or 2-naphthyl, especially 1-naphthyl.

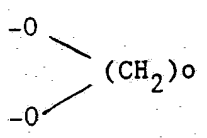
R_8 and R_9 when they are (C_{1-5})alkyl have the significances given above for alkyl, and when they are aryl, they signify phenyl, 1- or 2-naphthyl, preferably 1-naphthyl. The latter significance is preferred for R_8, while hydrogen is the preferred significance for R_9.

In the group $R_{10}O(CH_2CH_2O)_m-$, R_{10} preferably signifies methyl, n is preferably a whole number from 4 to 12, especially 7, and m is preferably 1.

The hydrophilic or lipophilic amino acid side chain in the definition of R_{11} may be for example a n-butyl, isobutyl, benzyl, 4-imidazolylmethyl, 2-methylthioethyl, cyclohexylmethyl or a pyridylmethyl radical.

When R_1 denotes (C_{1-5})alkyl, the alkyl radicals may be as defined above, and are especially methyl.

When R_2 denotes (C_{1-10})alkyl, it may be straight-chain or branched and signifies the above alkyl radicals, when it is a (C_{3-10})-cycloalkyl(C_{1-5})alkyl which is optionally substituted in the cycloalkyl moiety, it preferably signifies cyclohexylmethyl, whereby the cycloalkyl is optionally substituted by oxo, hydroxy or disubstituted (spiro-anellated) by a radical of formula



whereby o signifies 2 or 3 adamantyl, preferably 1-adamantylmethyl, when it is (C_{6-10})aryl-(C_{1-5})alkyl, it preferably signifies benzyl or naphthylmethyl, and when it is a

heteroarylalkyl radical, the heteroaryl moiety especially signifies pyridyl, thienyl or furyl radicals and the alkyl moiety is as defined above.

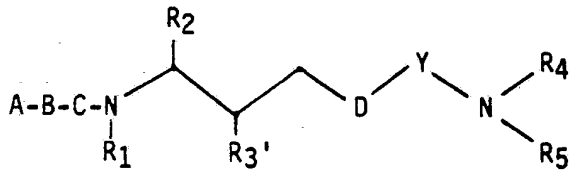
When R_4 and R_5 denote a (C_{6-10})aryl-(C_{1-5})-alkyl radical, they preferably signify a phenyl-(C_{1-5})-alkyl especially a benzyl radical, when they are a heteroarylalkyl radical, the heteroaryl moiety especially signifies a pyridyl, thienyl or furyl radical and alkyl denotes the above-mentioned radicals. When R_4 and R_5 denote (C_{1-5})alkyl, alkyl has the above-mentioned significances.

When R_{12} denotes a (C_{1-5})alkyl radical, alkyl signifies the above-mentioned radicals, but especially isopropyl, n-butyl, isobutyl and 2-methylbutyl. Hydroxyalkyl preferably signifies hydroxymethyl or hydroxyethyl. When R_{13} signifies aminomethyl-pyridyl, it is preferably aminomethyl-2-pyridyl.

In R_{14}, (C_{1-5})alkyl has the above-mentioned significances.

The preparation of compounds of formula I can be effected as follows:

a) Compound of formula Ia,



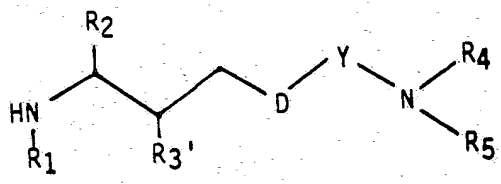
Ia

wherein A, B, C, D, Y, R_1, R_2, R_4 and R_5 are defined as above and R_3' is hydrogen, hydroxyl or a radical of formula $-OCOR_2$,

wherein R_2 is defined as above, may be obtained by reacting compounds of formula II,

A-B-C-OH II

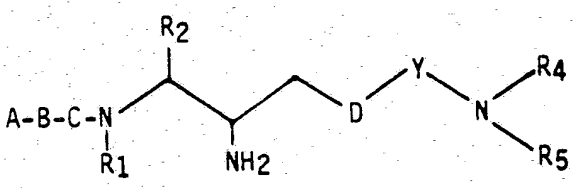
wherein A, B and C are defined as above,
with compounds of formula III



III

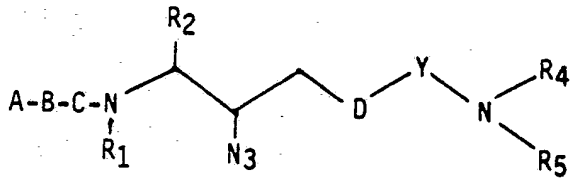
wherein R_1, R_2, R_3', R_4, R_5, Y and D are defined as above,

b) Compounds of formula Ib



Ib

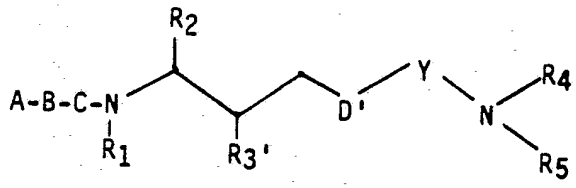
wherein A, B, C, D, Y, R_1, R_2, R_4 and R_5 are defined as above, are obtained by reducing compounds of formula IV



IV

wherein A, B, C, D, Y, R_1, R_2, R_4 and R_5 are defined as above and

c) Compounds of formula Ic

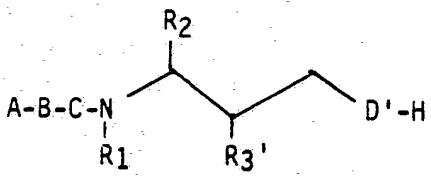


Ic

wherein A, B, C, Y, R_1, R_2, R_3', R_4 and R_5 are defined as above, and D' denotes -O- or  ,

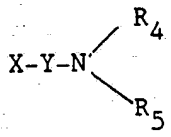
wherein R_1 is defined as above

are obtained by reacting compounds of formula V



V

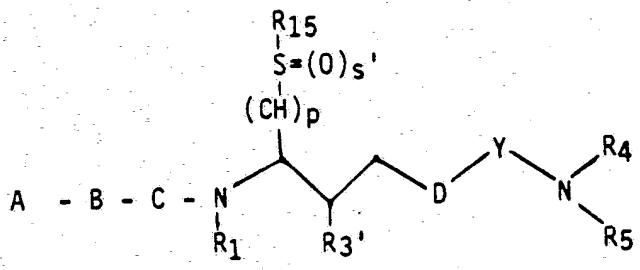
wherein A, B, C, D', R_1, R_2 and R_3' are defined as above with a compound of formula VI



VI

wherein Y, R_4 and R_5 are defined as above, and X signifies halogen, especially chlorine.

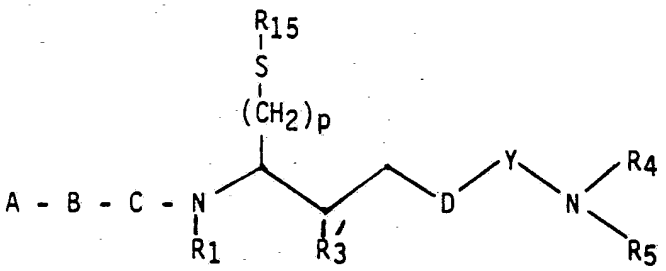
d) Compounds of formula Id



Id

wherein A, B, C, D, Y, R_1, R_3', R_4, R_5, R_{15} and p are defined as above and s' stands for 1 are obtained by oxidation of

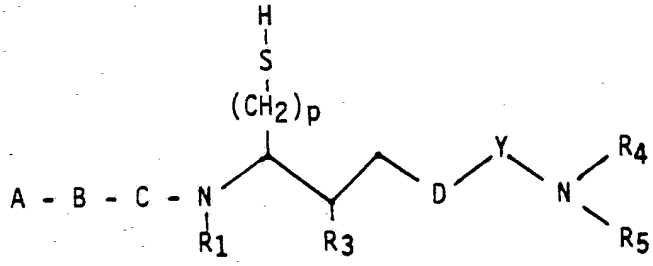
compounds of formula Ie



Ie

wherein A, B, C, D, Y, R_1, R_3', R_5, R_{15} and p are defined above

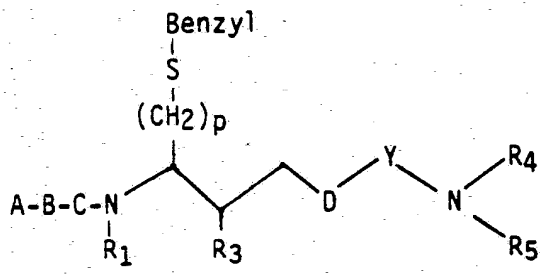
e) Compounds of formula If



If

wherein A, B, C, D, Y, R_1, R_3, R_4, R_5 and p are defined above are obtained by splitting off the benzyl group of compounds

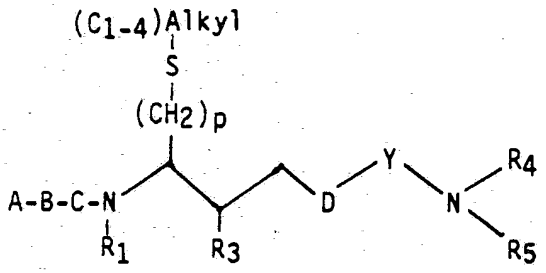
of formula Ig



Ig

wherein A, B, C, D, Y, R_1, R_3, R_4, R_5 and p are defined above,

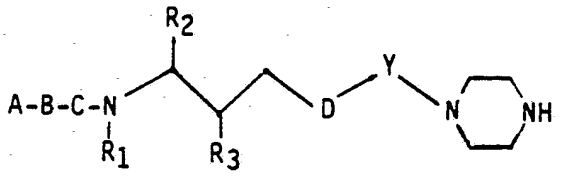
f) Compounds of formula Ih



Ih

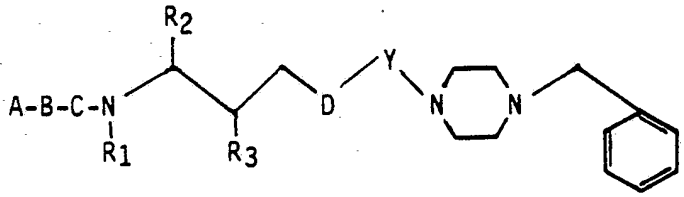
wherein A, B, C, D, Y, R_1, R_3, R_4, R_5 and p are defined above are obtained by introducing an alkylgroup in compounds of formula If as defined above.

g) Compounds of formula Ii



Ii

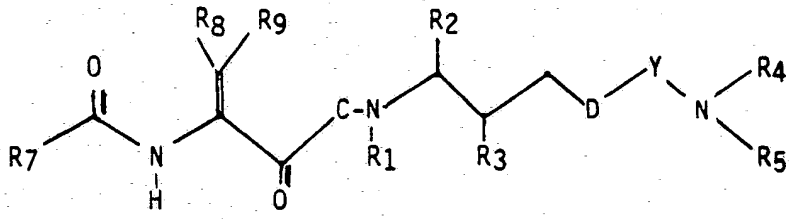
wherein A, B, C, D, Y, R_1, R_2 and R_3 are defined above are obtained by catalytically splitting off the benzyl group out of compounds of formula Ij



Ij

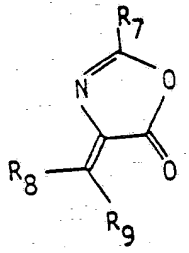
wherein A, B, C, D, Y, R_1, R_2 and R_3 are defined above.

h) Compounds of formula Ik



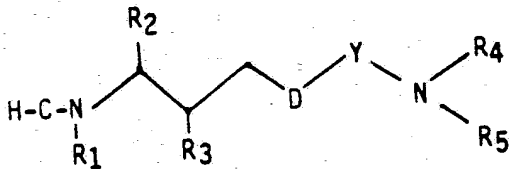
Ik

wherein C, D, Y, R_1 to R_5 and R_7 to R_9 are defined as above are obtained by reacting compounds of formula



IX

wherein R_7, R_8 and R_9 are defined as above with compounds of formula X



X

wherein C, D, Y, R_1 to R_5 are defined as above and obtained precursors of compounds of formula I are optionally transformed in compounds of formula I.

The process according to stage a) for the production of compounds of formula Ia is conveniently effected such that the compunds of formula II are reacted with the compunds of formula III in accordance with a method which is appropriate for peptide coupling. The reaction can take place for example in the presence of N,N'-dicyclohexylcarbodiimide or N-ethyl-N'-(Dimethylaminopropyl)-carbodiimide and N-hydroxysuccinimide or 1-hydroxybenzotriazole, whereby as the solvent e.g. dimethylformamide is used, and the reaction is carried out at temperatures of 0° to preferably room temperature. Alternately, the reaction may also be effected in the presence of 50% propanephosphonic acid anhydride in methylene chloride in the presence of a base such as N-methylmorpholine in a suitable solvent, e.g. dimethylformamide. In this case also, the reaction is conveniently effected at temperatures of 0°C to room temperature, preferably at room temperature.

The reduction of the compounds of formula IV according to stage b) takes place by known processes, for example by means of catalytical hydrogenation in the presence of an appropriate catalyst, e.g. palladium on active charcoal, in a suitable solvent such as ethanol, at temperatures of 0° to ca. 50°C, preferably at room temperature, and at pressures of 1 to 5 atm., preferably 1 atm.

The reaction, described in stage c), of compounds of formula V with compounds of formula VI conveniently takes place in the presence of a base, e.g. triethylamine or N-methylmorpholine, in an inert solvent such as tetrahydrofuran or dimethylformamide, at temperatures of ca. 0° to ca. 50°C, preferably at room temperature. Y being C = 0 the reaction may also take place with the corresponding isocyanate $R_4N = C = 0$ whereby compounds of formula

I, wherein R_5 signifies hydrogen are obtained.

In process d) the oxidation is effected by means of an oxidating agent e.g. hydrogen peroxide, acting upon compounds of formula Ie in an acid solvent e.g. a 100% acetic acid at temperatures below room temperature e.g. 10°C.

The process according to stage e) is effected by reacting sodium in liquid ammonia at temperatures of -40°C environ with compounds of formula Ig whereby the benzyl-group is split off. The starting compounds of formula Ig may be obtained from appropriate starting compounds according to process c).

The process according to stage f) is an alkylating process whereby compunds of formula If are first reacted at -40°C environ with sodium in liquid ammonia and then with an (C_{1-4})alkylhalogenide esp. (C_{1-4})alkylbromide.

The catalytical cleavage of the benzyl-group from compounds of formula Ij according to stage g) is effected in presence of a palladium (10% on charcoal) catalyst in an appropriate solvent e.g. ethanol at a hydrogen pressure of 1 to 5 at. at temperatures up to 60°C environ, preferably at room temperature.

The reaction of an azlacton of formula IX with compounds of formula X according to process h) is effected according to methods known from the literature e.g. in an appropriate solvent like tetrahydrofuran or chloroform optionally in presence of an acylating catalyst like 4-dimethylaminopyridin at temperatures from 0° to 80°C environ, preferably at roomtemperature or reflux temperature of tetrahydrofuran or chloroform.

The starting compounds used in the above processes are either known (see for example E. Wünsch in: Houben-Weyl, "Methoden der

organischen Chemie", Volume XV/1 and XV/2, "Synthese von Peptiden", Georg Thieme, Stuttgart, 1984) or may be produced in known manner, for example as described in the following examples.

The compounds of formula I produced according to the invention may be isolated and purified in known manner. Racemic and/or diastereoisomeric mixtures can be separated in known manner.

If the compounds of formula I contain acidic or basic groups, these can also optionally form salts, for example metal salts such as sodium salts or acid addition salts such as hydrochlorides.

In the following examples all temperatures are given in °C and are uncorrected.

Example 1: **(2R,3S)-3-(tert-butyloxycarbonylamino)-4-cyclohexyl-2-hydroxybutane-sulphonic acid dimethylamide**

4 g of methanesulphonic acid dimethylamide are dissolved in 50 ml of tetrahydrofuran, and mixed at 0-5° with 20 ml of n-butyllithium (1.6 M in hexane). After ½ hour hour, 3.7 g of N-tert.-BOC-cyclohexylalaninal is added at once. After ½ hour, the reaction mixture is poured onto ether/2N aqueous tartaric acid, the org. phase is separatet, dried with magnesium sulphate and the solvent is evaporated off under vacuum. The crude product is chromatographed on silica gel with ether/hexane 30-70%. The main product is obtained as a colorless oil, which solidifies upon standing. M.p. 86-87°. The (2R,3R) isomer is obtained as a by-product.

Example 2: **(2R,3S)-3-(tert-butyloxycarbonylamino)-4-(1,4-dioxaspiro[4,5]undec-8-yl)-2-hydroxybutane-sulphonic acid dimethylamide**

The title compound is obtained analogously to example 1 from 5.2 g of methanesulphonic acid dimethylamide, 26 ml of n-butyllithium and 6 g of the corresponding aldehyde. M.p. 48-50°.

Example 3: **(2R,3S)-3-(tert-butyloxycarbonylamino)4-cyclohexy-2-azido-butanesulphonic acid dimethylamide**

1 g of the by-product of Example 1 (2R,3R isomer) is dissolved in 10 ml of toluene, and mixed at -30° with 1.5 g of triphenylphosphine, 30 ml of ammonia (ca. 1N solution in benzene) and 0.9 ml of azodicarboxylic acid diethylester. The reaction mixture is stirred over night at room temperature and then filtered off over silica gel. An inseparable mixture of the title compound and (3S)-(tert-butyloxycarbonyl)-4-cyclohexyl-1-butene-sulphonic acid dimethyl-

amide is obtained.

Example 4: **(2R,3S)-3-(tert-butyloxycarbonylamino)-2-hydroxy-4-(2-naphthyl)-butane-sulphonic acid dimethylamide**

The title compound is obtained analogously to Example 1, as a colourless oil, from 1.7 g of methanesulphonic acid dimethylamide, 8.5 ml of butyllithium and 2 g of the corresponding aldehyde.

Example 5: **(2R,3S)-3-(tert-butyloxycarbonylamino)2-hydroxy-5-methyl-hexane-sulphonic acid dimethylamide**

The title compound is obtained analogously to Example 1, as a diasteroisomeric mixture (ca. 2:1), from 4 g of methanesulphonic acid dimethylamide, 60 ml of n-butyllithium and 4 g of N-tert-BOC-leucinal.

Example 6: **(3S,4S)-4-(tert-butyloxycarbonylamino)-5-cyclohexyl-3-hydroxy-pentane-sulphonic acid dimethylamide**

1 g of methanesulphonic acid dimethylamide is dissolved in 10 ml of tetrahydrofuran. 5.1 ml of n-butyllithium are added in drops at 0-5°. After ½ hour, 1 g of (2S)-2-((1S)-tert-butyloxy-carbonyl-amino-2-cyclohexyl-ethyl)oxirane is added. After 20 mins., the mixture is partitioned between ether and 2N aqueous tartaric acid, the organic phase is separated, dried and concentrated by evaporation. The crude product is recrystallised from methylene chloride/hexane. M.p. 110-111°.

Example 7: **(1S,3S,4S)-4-(tert-butyloxycarbonylamino)-5-cyclohexyl-3-hydroxy-1-isopropyl-pentane-sulphonic acid-dimethylamide**

The title compound is obtained analogously to example 6, as a diastereoisomeric mixture (ca. 1:5), from 0.4 g of isobutane-sulphonic acid dimethylamide, 1.5 ml of n-butyllithium and 200 mg of epoxide.

Example 8: **(2R,3S)-3-(N-BOC-phenylalanyl-phenylalanyl)amido-4-cyclohexyl-2-hydroxy-butane-sulphonic acid dimethylamide**

330 mg of the sulphonic acid amide of example 1 are dissolved in 1 ml of methylene chloride, and 1 ml of trifluoroacetic acid is added. After 1 hour, the mixture is partitioned between 2N aqueous sodium carbonate solution and methylene chloride, the organic phase is separated, dried with potassium carbonate and concentrated by evaporation. Then, 230 mg of BocPhePheOH, 225 mg of HOBT and ca. 5 ml of methylene choride are added. The mixture is cooled to 0-5°, 170 mg of dicyclohexylcarbodiimide are added, and stirring is effected for ca. 15 hours at room temperature. The precipitated dicyclohexylurea is filtered off, and the crude product is chromatographed on silica gel with ether/methylene chloride 50-90%. $[\alpha]D^{20}$ = -29.1° (c = 0.6 in $CH_2CH_2)_2$).

Example 9: **(2R,3S)-3-(N-BOC-β-cyclohexylalanyl-β-cyclohexyl-alanyl)amido-4-cyclohexyl-2-hydroxy-butane-sulphonic acid-dimethylamide**

50 mg of the product of example 8 are dissolved in 5 ml of ethanol, and hydrogenated for 24 hours at 40°/2 atm hydrogen over

Rh-Alox (5%). The catalyst is filterded off and the product is lyophilised from benzene. $[\alpha]D^{20}$ = -46.1° (c = 0.6 in CH_2Cl_2).

Example 10: **(2R,3S)-3-(N-BOC-phenylalanyl-norleucyl)amido-4-cyclohexyl-2-hydroxy-butane-sulphonic acid-dimethylamide**

160 mg of BOC-SO_2-Chatin-NMe_2 (Example 1) are reacted with 100 mg of BOCPheNleOH, 100 mg of Hydroxybenzotriazole and 80 mg of Dicyclohexylcarbodiimide analogously to Example 8. $[\alpha]D^{20}$ = -32.4° (c = 0.2 in CH_2Cl_2).

Example 11: **(2R,3S)-3-(N-BOC-β-cyclohexylalanyl-norleucyl)-amido-4-cyclohexyl-2-hydroxy-butane-sulphonic acid dimethylamide**

20 mg of the product of example 10 are hydrogenated exactly as in Example 9. $[\alpha]D^{20}$ = -38.2° (c = 0.1 in CH_2Cl_2).

Example 12: **(2R,3S)-3-(N-BOC-phenylalanyl-histidyl)amido-4-cyclohexyl-2-hydroxy-butane-sulphonic acid dimethylamide**

225 mg of BOC-SO_2-Chatin-NMe_2 (Example 1) are reacted with 236 mg of BOCPheHisOH, 160 mg of hydroxybenzotriazole and 120 mg of dicyclohexylcarbodiimide analogously to Example 8. For peptide coupling, dimethylformamide is used instead of methylene chloride. After chromatography MeOH/CH_2Cl_2, 0-10%, two diastereoisomers are obtained: diastereoisomer A: $[\alpha]D^{20}$ = -32.2° (c = 0.2 in CH_2Cl_2/MeOH 9:1; diastereoisomer B: $[\alpha]D^{20}$ = -26.0° (c = 0.6 in CH_2Cl_2/MeOH 9:1).

Example 13: **(2R,3S)-3-[N-(bis-(1-naphthylmethyl)acetyl)norleucyl]amido-4-cyclohexyl-2-hydroxy-butane-sulphonic acid-dimethylamide**

200 mg of BOC-SO_2-ChatinNMe_2 (Ex. 1) are reacted with 240 mg of N-(bis-(1-naphthylmethyl)acetyl)-Nle-OH, 140 mg of hydroxybenzotriazole and 110 mg of dicyclohexylcarbodiimide, analogously to Example 8. $[\alpha]D^{20}$ = -43.9° (c = 0.2 in CH_2Cl_2).

Example 14: **(2R,3S)-3-(N-BOC-phenylalanyl-norleucyl)amido-2-amino-4-cyclohexyl-butane-sulphonic acid-dimethylamide**

150 mg of the sulphonic acid amide mixture of Example 3 are reacted with 100 mg of BOCPheNleOH, 700mg of hydroxybenzotriazole and 80 mg of dicycloxylcarbodiimide analogoulsy to Example 8. The crude product is dissolved in ethanol and hydrogenated for 4 hours at 20°/1 atm. hydrogen over Pd/C (10%). Chromatography on silica gel with MeOH/CH_2Cl_2 0-5% yields the title compound $[\alpha]D^{20}$ = -37.1° (c = 0.2 in CH_2Cl_2) as well as BOC-Phe-Nle-SO_2-desoxy-chatin-NMe_2 $[\alpha]D^{20}$ = -26.4° (c = 0.2 in CH_2Cl_2).

Example 15: **(2R,3S)-3-(N-BOC-phenylalanyl-norleucyl)amido-4-(1,4-dioxaspiro[4.5]undec-8-yl)-2-hydroxy-butane-sulphonic acid-dimethylamide**

335 mg of the sulphonamide of Example 2 are reacted with 290 mg of BOC-Phe-NleOH, 200 mg of hydroxybenzotriazole and 158 mg of dicyclohexylcarbodiimide analogously to Example 8. $[\alpha]D^{20}$ = -32.6° (c = 0.2 in CH_2Cl_2)

Example 16: **(2R,3S)-3-(N-BOC-phenylalanyl-norleucyl)amido-4-(4'-oxocyclohexyl)-2-hydroxy-butane-sulphonicacid dimethylamide**

200 mg of the product of Ex. 15 are dissolved in 10 ml of tetrahydrofuran/Water, and mixed with a few drops of conc. hydrochloric acid. After 10 hours, the mixture is partitioned between ethyl acetate and aqueous Na bicarbonate solution, the organic phase is separated, dried and concentrated by evaporation. $[\alpha]D^{20} = -45.6°$ (c = 0.2 in CH_2Cl_2).

Example 17: **(2R,3S)-3-(N-BOC-phenylalanyl-norleucyl)amido-4-(4'-oxocyclohexyl)-2-hydroxy-butane-sulphonic acid-dimethylamide**

70 mg of the product of Example 16 are dissolved in 5 ml of methanol. 10 mg of sodium borhydride are added, stirred for 15 mins. at room temperature, and then partitioned between ethyl acetate and 2N aqueous sodium carbonate solution.
$[\alpha]D^{20} = -31.1°$ (c = 0.2 in CH_2Cl_2).

Example 18: **(3S,4S)-4-(N-BOC-phenylalanyl-norleucyl)amido-5-cyclohexyl-3-hydroxy-pentane-sulphonic acid-dimethylamide**

135 mg of the sulphonamide of Example 6 are reacted with 75 mg of BOC-Phe-Nle-OH, 70 mg of hydroxybenzotriazole and 52 ml of dicyclohexylcarbodiimide analogously to Example 8.
$[\alpha]D = -10°$ (c = 0.2 in CH_2Cl_2)

Example 19: (1S,3S,4S)-4-(N-BOC-phenylalanylnorleucyl)amido 5-cyclohexyl-3-hydroxy-1-isopropyl-pentane-sulphonic acid dimethylamide

47 mg of the diastereoisomeric mixture of Example 7 are reacted with 40 mg of BOCPhe-Nle-OH, 28 mg of hydroxybenzotriazole and 22 mg of dicyclohexylcarbodiimide analogously to Example 8. Chromatography on silica gel with ether/hexane 50-100% yields two diastereoisomers: A: $[\alpha]D^{20} = -36.4°$, B: $[\alpha]D^{20} = -10,0°$ (c = 0.1 in CH_2Cl_2).

Example 20: (2R,3S)-3-(N-BOC-phenylalanyl-norleucyl)amido-2-hydroxy-4-(2-naphthyl)-butane-sulphonic acid-dimethylamide

130 mg of sulphonamide of Example 4 are reacted with 115 mg of BOC-PheNleOH, 85 mg of hydroxybenzotriazole and 65 mg of dicyclohexylcarbodiimide analogously to Example 8.
$[\alpha]D^{20} = -43.7°$ (c = 0.2 in CH_2Cl_2).

Example 21: (2R,3S)-3-[N-(bis-(1-naphthylmethyl)acetyl)-norleucyl]amido-2-hydroxy-5-methyl-hexane-sulphonic acid-dimethylamide

100 mg of the diastereoisomieric mixture of Example 5 are reacted with 70 mg of BOCPheNleOH, 70 mg of hydroxybenzotriazole and 51 mg of dicyclohexylcarbodiimide analogously to Example 8.
The product is obtained as an inseparable diastereoisomeric mixture (ca. 2:1).

Example 22: **(2S,3S)- and (2R,3S)-3-(BOC-phenylalanyl-norleucyl)-amido-4-cyclohexyl-1-isobutyl-sulphamoylamino-2-butanol**

A solution of 94 mg of isobutylsulphamoyl chloride in 1 ml of dioxane is added to a mixture of 273 mg of (2S,3S)-3-BOC-phenylalanyl-norleucinyl)amido-1-amino-4-cyclohexyl-2-butanol and 0.1 ml of triethylamine in 11 ml of dioxane, and the mixture obtained is stirred for 20 hours at room temperature and subsequently concentrated under vacuum. The residue is dissolved in ethyl acetate and the solution is washed with diluted hydrochloric acid, an aqueous sodium bicarbonate solution and aqueous sodium chloride solution. Drying over anhydrous sodium sulphate, evaporation under vacuum and chromatography (silica gel with dichloromethane/-methanol 40:1 as eluant) yields the compound named in the title as an amorphous solid, $[\alpha]D^{20} = -7°$ (c = 0.5 in dichloromethane).

Using (2R,3S)-3-(BOC-phenylalaninyl-norleucinyl)amido-1-amino-4-cyclohexyl-2-butanol in accordance with the same process, (2R,3S)-3-(BOC-phenylalaninyl-norleucinyl)-amido-4-cyclohexyl-isobutyl-sulphamoylamino-2-butanol is obtained as an amorphous solid, $[\alpha]D^{20} = -3.2°$ (c = 0.5 in dichloromethane).

The starting compounds used in this process are obtained as described in the following:

a) (3S)-3-BOC-amido-4-cyclohexyl-1-nitro-2-butanone

(intermediate product 1)

A solution of 32.6 ml of nitromethane in 160 ml of tetrahydrofuran and 160 ml of hexamethylphosphoric acid triamide is added whilst cooling with ice and stirring vigorously to a suspension of 18.0 g of sodium hydride (80% in mineral oil)

in 180 ml of tetrahydrofuran. The solution obtained is stirred for 1 hour at room temperature, then cooled to 0°, and a solution of 69.9 g of N-BOC-L-β-cyclohexyl-alanine-3,5-dimethylpyrazolide in 700 ml of tetrahydrofuran is added. After stirring for 20 hours, the mixture is mixed with 600 ml of 1N hydrochloric acid, extracted twice with ether, the combined organic extracts are washed with aqueous sodium chloride solution, dried over anhydrous sodium sulphate and evaporated under vacuum. After chromatography of the crude product on silica gel using toluene/ethyl acetate (6:1) as the eluant, the above intermediate product 1 is obtained as colourless crystals having a m.p. of 97-98°.

b) (2S,3R)- and (2R,3S)-3-BOC-amino-4-cyclohexyl-1-nitro-2-butanol

(intermediate compounds 2A and 2B)

2.27 g of sodium borohydride are added in small portions to an ice-cooled solution of 18.9 g of intermediate product 1 obtained above in 190 ml of ethanol. Stirring is then effected for one hour without cooling, after which the pH value of the solution is adjusted to 3 by adding 10% aqueous tartaric acid and cooling, the solution is evaporated under vacuum, extracted twice with ether, the combined organic phases are washed with aqueous sodium chloride solution, dried over anhydrous sodium sulphate and evaporated under vacuum. Treatment of the remaining oily mixture of two diastereoisomers with ether/hexane yields isomer 2B which has a m.p. of 116-118° (decomp.). Chromatography of the mother solution on silica gel using hexane/ether (2:1) as the eluant yields isomer 2B as an oil.

Rf values (silica gel, hexane/ether 2:1): 2A, 0.136:2B, 0.106.

c) (2S,3S)- and (2R,3S)-1-amino-3-BOC-amino-4-cyclohexyl-2-butanol

(intermediate compounds 3A and 3B)

5.96 g of ammonium formate are added in small portions over the course of 1 hour, in an inert atmosphere, to a mixture of 7.5 g of intermediate compound 2A, which was obtained as described above, and 0.75 g of palladium (10% on animal charcoal) in 50 ml of methanol. After stirring for 17 hours at room temperature, the suspension is filtered through celite and the filtrate is evaporated under vacuum. The residue is taken up in 2N hydrochloric acid, washed twice with ether and the aqueous phase is rendered alkaline by adding sodium bicarbonate. The aqueous phase is extracted twice with ethyl acetate, the organic phases combined, dried over anhydrous sodium sulphate and evaporated under vacuum. The foamy residue is transformed into the hydrogen oxalate and is crystallised from ether. The hydrogen oxalate of intermediate compound 3A is obtained with a m.p. of 165-166° (decomp.).

The hydrogen oxalate of intermediate compound 3B, which is obtained analogously from intermediate compound 2B, melts at 137-138° (decomp.).

d) (2S,3S)- and (2R,3S)-3-BOC-amino-1-Cbz-amino-4-cyclohexyl-2-butanol

(intermediate compounds 4A and 4B)

4.18 ml of benzyl chloroformate are added at a temperature of 2 to 5° to a solution of 5.28 ml of triethylamine and 6.3 g of intermediate compound 3A, which was obtained as in the above process, in 120 ml of dichloromethane, and the solution obtained is stirred for 30 minutes at room temperature. It is then diluted with dichloromethane and washed with 0.25N hydrochloric acid, saturated aqueous sodium bicarbonate solution and water. The organic phase is dried over sodium sulphate and evaporated under vacuum. Chromatography of the residue on silica gel using toluene/ ethyl acetate (3:1) as the eluant yields intermediate compound 4A as a slightly yellowish oil.

Intermediate compound 4B is obtained as an oil from intermediate compound 3B, using the same process.

e) (2S,3S)- and (2R,3S)-3-amino-1-Cbz-amino-4-cyclohexyl-2-butanol (intermediate compounds 5A and 5B)

8.06 g of intermediate compound 4A are added whilst cooling to 80 ml of the mixture of acetic acid/conc. hydrochloric acid (9:1), and the solution obtained is stirred for 1 hour at room temperature and then evaporated to dryness. The hydrochloride of intermediate compound 5A is hereby obtained as a colourless foam.

The hydrochloride of intermediate compound 5B is obtained from intermediate compound 4B using the same process.

f) (2S,3S)- and (2R,3S)-3-(BOC-phenylalaninyl-norleucinyl)-amino-1-Cbz-amino-4-cyclohexyl-2-butanol

4.06 ml of diphenylphosphorylazide and 4.94 ml of triethylamine are added gradually to an ice-cooled solution of 6.68 g of BOC-Phe-Nle-OH and 6.3 g of crude hydrochloride of intermediate compound 5A in dimethylformamide, and the clear solution obtained is stirred over night at room temperature, then concentrated under vacuum, taken up in dichloromethane and the dichloromethane solution is washed with 0.25N hydrochloric acid, saturated aqueous sodium bicarbonate solution and water, and dried over anhydrous sodium sulphate. After evaporation under vacuum, the residue is chromatographed on silica gel (dichloromethane/ethanol 49:1 as the eluant) and the product obtained is crystallised from dichloromethane/hexane. Intermediate product 6A thus obtained melts at 167-168° (decomp.).

Intermediate compound 6B which has a m.p. of 150-151° (decomp.) is obtained from intermediate compound 5B using the same process.

g) (2S,3S)- and (2R,3S)-1-amino-3-(BOC-phenylalaninyl-norleucinyl)-amino-4-cyclohexyl-2-butanol

(intermediate compounds 7A and 7B)

7.0 g of intermediate compound 6A and 0.7 g of palladium on active charcoal (10%) in 140 ml of methanol are hydrogenated for 1.5 hours at room temperature in a hydrogen atmosphere at atmospheric pressure, and the mixture is subsequently diluted

with dichloromethane and filtered through celite. After evaporation of the filtrate under vacuum and crystallisation of the residue from methanol/ether, intermediate compound 7A is obtained as colourless crystals having a m.p. of 140-141°, $[\alpha]D^{20}$ = -38.5° (c = 1 in methanol).

Intermediate compound 7B is obtained as colourless crystals having a m.p. of 168-169 (decomp.) from intermediate compound 6B, using the same process.
$[\alpha]D^{20}$ = -25.6° (c = 1 in methanol).

Example 23: **(2S,3S)-3-(BOC-phenylalaninyl-norleucyl)amido-4-cyclohexyl-1-dimethylsulphamoylamino-2-butanol**

The title compound is obtained analogously to example 22, using dimethylasulphamoyl chloride instead of isobutylsulphamoyl chloride. $[\alpha]D^{20}$ = -11° (c = 0.1 in CH_2Cl_2).

Example 24: **(2R,3S)-3-(N-benzoyl-dehydrophenylalaninyl-norleucyl)-amido-1-dimethylsulphamoyl-amino-5-methyl-2-hexanol**

The title compund is obtained as a diastereoisomeric mixture (ca. 2:1) having a m.p. of 194-196° (decomp.) analogously to Example 21, using N-benzoyldehydrophenylalaninyl-norleucine insead of BOC-Phe-Nle-OH.

Example 25: **N-(3-cyclohexylpropionyl)-norleucine**

A solution of 1.92 g of 3-cyclohexylpropionic acid chloride in 22 ml of ether is added whilst cooling with ice to a solution of

1.31g of norleucine in 22 ml of 1N aqueous sodium hydroxide, and the mixture is stirred for 1 hour at 0°C. The mixture is subsequently acidified with 0.25N hydrochloric acid, extracted twice with ether, the combined organic phases are washed with saturated sodium chloride solution, dried over sodium sulphate and concentrated by evaporation under vacuum. Crystallisation of the residue from ether/hexane yields the title compound which has a m.p. of 138-139°C.

Example 26: **(2S,3S)-3-(3-cyclohexyl-propionyl-norleucyl) amido-1-Cbz-amino-4-cyclohexyl-2-butanol**

The title compound is obtained as an amorphous substance analogously to Example 22 f), using 3-cyclohexyl-propionyl-norleucine (Ex. 25) instead of BOC-Phe-Nle-OH.

Example 27: **(2S,3S)-3-(3-cyclohexyl-propionyl-norleucyl) amido-1-amino-4-cyclohexyl-2-butanol**

The title compound is obtained as an amorphous substance analogously to Example 22 g), by means of hydrogenation of the compound of Example 26.

Example 28: **(2S,3S)-3-(3-cyclohexyl-propionyl-norleucyl) amido-4-cyclohexyl-1-dimethylsulphamoylamino-2-butanol**

The title compound is obtained as an amorphous substance analogously to Example 22, using (2S,3S)-3-cyclohexyl-propionyl-norleucyl)amido-1-amino-4-cyclohexyl-2-butanol and dimethyl-

sulphamoyl chloride, $[\alpha]D^{20} = -25.7°$ (c = 1 in methanol) (sinters from 78°C).

INTERMEDIATE PRODUCTDS:

N-(bis-1-naphthylmethyl)-acetyl-Nle-OH

660 mg of bis-(1-naphthylmethyl)-acetic acid and 280 mg of norleucine-methylester are dissolved in methylene chloride and cooled to 0°. 400 mg of dicyclohexylcarbodiimide are added and stirred for ca. 15 hours at room temperature. The precipitated dicyclohexylurea is filtered off, the filtrate concentrated by evaporation, dissolved in methanol and mixed with 200 mg of sodium hydroxide (dissolved in water). After 2 hours, the mixture is acidified with 2N hydrochloric acid, extracted with methylene chloride, dried and concentrated by evaporation. The crude product is recrystallised from methylene chloride/hexane. M.p. 157-159°.

Bis-(1-naphthylmethyl)-acetic acid

4.6 g of sodium are dissolved in 100 ml of ethanol. 16 g of malonic acid diethylester and 40 g of 1-chloromethylnaphthalene are added. The mixture is then refluxed for 24 hours, cooled and the precipitated salts are dissolved by adding ice water. The organic phase is separated, the aqueous phase extracted with ether, and the combined organic phases dried over magnesium sulphate and concentrated by evaporation. The crude product is added to a mixture of 50 ml of water, 700ml of ethanol and 20 g of potassium hydroxide and refluxed for 4 hours. It is then cooled, acidified with conc. hydrochloric acid and extracted with ether. The ether solution is dried, concentrated by evaporation and the

residue heated to 180-200°. After cooling to room temperature, the glassy residue is dissolved in methylene chloride and precipitated with hexane. M.p. 171-172°C.

(1-tert-butyloxycarbonylamino-6-cyclohexyl-ethyl)-oxirane

6 g of sodium hydride dispersion (80% in white oil) are suspended in a mixture of 60 ml of dimethyl sulphoxide and 30 ml of tetrahydrofuran. The suspension is cooled to 0-5°, and a solution of 13 g of trimethylsulphonium iodide in 50 ml of dimethyl sulphoxide is added in drops. After 10 mins, 50 ml of t-BOC-cyclohexylalaninal (0.54 M in toluene) are added, and the temperature is allowed to rise to room temperature. The reaction mixture is diluted with ice water, the org. phase separated, washed 4x with water, dried over magnesium sulphate and concentrated by evaporation. Chromatography on silica gel with ether/hexane 10-30% yields the title compound, together with a little of the diastereoisomer (ratio ca. 3:1). M.p. 58-59°C.

Example 29: **(2R,3S)-3-[N-1-adamantyl)propionyl)norleucyl]-amido-4-cyclohexyl-2-hydroxy-butane-sulphonic acid-dimethylamide**

The title compound is obtained analogously to Example 8 using N-[3-(1-adamantyl)propionyl]-norleucin instead of BOCPhePheOH. $[\alpha]D^{20}$ = -25,7° (c = 1 in methanol).

The starting compound adamantyl-propionyl norleucin, m.p. 119-120° is prepared analogously to Example 25 starting from adamantyl propinonyl chloride and norleucin.

Example 30: **(2R,3S)-3-(N-BOC-β-cyclohexylalanylhistidyl)amido-4-cyclohexyl-2-hydroxy-butane-sulphonic acid-dimethylamide**

The title compound is obtained analogously to Example 8 reacting 190 mg BOC-SO_2-Chatin-$N(Me)_2$ - Example 1 - with 201 mg BOC-Cha-His-OH, in presence of 70 mg hydroxybenzotriazol and 102 dicyclohexyl carbodiimid. The crude product is chromatographed on silicagel (methanol/methylenechloride 1-10% as the eluant). $[\alpha]_D^{20}$ = -38,9° (c = 0.2 in methylenchloride).

Example 31: **(2R,3S)-3-[N]-(bis-(1-naphthylmethyl)acetyl) histidyl]amido-4-cyclohexyl-2-hydroxy-butane-sulphonic acid-dimethylamide**

80 mg BOC-SO_2-Chatin-N Me_2 (Example 1) are reacted analogously to Example 8 with 100 mg N-(bis-(7-naphthylmethyl)-acetyl)-Nle-OH in presence of 50 mg hydroxybenzotriazol and 44 mg dicyclohexylcarbodiimid. The obtained crude product is chromatographed on silicagel using methanol/methylenchloride 1-10% as the eluant. $[\alpha]_D^{20}$ = -17,1° (c = 0.2 in methylenechloride).

Example 32: **(2R,3S)-3-[N-BOC-β-(2,1,3-benzoxadiazol-4-yl)alanyl-norleucyl]amido-4-cyclohexyl-2-hydroxy-butane-sulphonic acid dimethylamide**

96 mg BOC-SO_2-Chatin-NMe_2 (Example 1) are reacted analogously to Example 8 with 98 mg BOC-BOL-NLE-OH in presence of 35 mg hydroxy-benzotriazol and 50 mg dicyclohexylcarbodiimid. The crude product is recristallised from methylenchlorid/hexan. $[\alpha]_D^{20}$ = -52,4° (c = 0.2 in methylenchloride).

Example 33: **(2R,3S)-3-(N-[2-methoxy-poly(2-ethoxy)acetyl] phenylalanyl-norleucyl)amido-4-cyclohexyl-2-hydroxy-butane-sulphonic acid dimethylamide**

35 mg H-Phe-HIS-SO_2-Chatin-NMe_2 are reacted with 60 mg of a mixture of oligomers of polyethylenglycolic acids (MW $\sim$ 350) in presence of 13 mg dicyclohexylcarbodiimide and 10 mg hydroxy benzotriazol in methylenechloride and the reaction product is purified by chromatography on silicagel (using methanol/methylenechloride 5-10% as the eluent).

Example 34: **(2R,3S)-3-[N-(bis-(1-naphthylmethyl)acetyl)-methionyl]amido-4-cyclohexyl-2-hydroxy-butane-sulphonic acid-dimethylamide**

165 mg BOC-SO_2-Chatin-NMe_2 (Example 1) are reacted analogously to Example 8 with 203 mg N-(bis-(7-naphthylmethyl)acetyl)-Met-OH in presence of 115 mg hydroxybenzotriazol and 90 mg dicyclohexylcarbodiimid. $[\alpha]_D^{20}$ = -45,3° (c = 0.1 in methylenechloride).

Example 35: **(2R,3S)-3-[N-(bis-(1-Naphthylmethyl)acetyl)methion (D,L-S-oxid)yl]amido-4-cyclohexyl-2-hydroxy-butane-sulphonic acid dimethylamide**

20 mg of the title compound of Example 34 are dissolved in glacial acetic acid and to the solution 10 mg sodiumperborate are added. After 1 hour the mixture is distributed between methylenechloride and a saturated aqueous sodiumbicarbonate-solution. The organic phase is dried and evaporated. The title product is obtained as a 1:1 diastereomer mixture.

Example 36: (2R,3S)-3-(N-BOC-phenylalanyl-norleucyl)amido-4-(1-adamantyl)-2-hydroxy-butane-sulphonic acid-dimethylamide

69 mg BOC-SO_2-Adatin-NMe_2 are reacted analogously to Example 8 with 61 mg BOC-Phe-Nle-OH in presence of 64 mg hydroxybenzotriazol and 62 mg N-ethyl-N-(3-dimethylaminopropyl)-carbodiimid (EDCI). The crude product is chromatographed on silicagel using hexane/-ethylacetate (1:1) as eluent. The title compound is according to ^{1}H-NMR a mixture of diastereomeres (2R,3S:2S,3S = 60:40.

The starting product BOC-SO_2-Adatin-NMe_2 (60 to 40 mixture of diastereomeres) is prepared analogously to Example 1 reacting N-tert. BOC-Adamantylalaninal and methansulphonic acid dimethyl-amide.

Example 37: (2R,3S)-3-(N-BOC-phenylalanyl-norleucyl)-amido-5,5-dimethyl-2-hydroxy-hexane-sulphonic acid-dimethylamide

235 mg BOC-SO_2-Neotin-NMe_2 are reacted analogously to Example 8 with 180,3 mg BOC-Phe-Nle-OH in presence of 198 mg hydroxy-benzotriazol and 187 mg EDCI (see Example 36). The crude product is chromatographed on silicagel using hexane/ethylacetate (1:2) as eluent. After recristallisation from hexan/ethylacetate yields the title product as a mixture of diastereomeres (2R,3S:2S, 3S = 65:35) having a melting point of 159 to 163°C.

The starting compound BOC-SO_2-Neotin-NMe_2 (A 65 to 35 mixture of diastereomeres)is prepared analogously to Example 1 from N-tert. BOC-neopentalglycinal and methanesulphonic acid dimethylamide.

Example 38: **(2R,3S)-3-(N-BOC-phenylalanyl-norleucyl)amido-4-cyclohexyl-2-hydroxy-butane-sulphonic acid-pyrrolidinamide**

The title product is obtained analogously to Example 8 reacting BOC-SO_2-Chatin-pyrrolidin with BOC-Phe-Nle-OH. $[\alpha]_D^{20}$ = -30.0° (c = 0.28 in ethanol).

The starting compound BOC-SO_2-chatin-pyrrolidine is obtained analogously to Example 1 from BOC-cyclohexylalaninal and methyl-sulphonyl-pyrrolidine.

Example39: **(2R,3S)-3-(N-BOC-phenylalanyl-norleucyl)amido-4-cyclohexyl-2-hydroxy-butane-sulphonic acid-piperidineamide**

The title product is obtained analogously to Example 8 from BOC-SO_2-Chatin-piperidine and BOC-Phe-Nle-OH. $[\alpha]_D^{20}$ = -32.6° (c = 0.27 in ethanol).

The starting product BOC-SO_2-Chatin-piperidine is obtained analogously to Example 1 from BOC-cyclohexylalaninal and methylsulphonyl piperidine.

Example 40: **(2R,3S)-3-(N-BOC-phenylalanyl-norleucyl)amido-4-cyclohexyl-2-hydroxy-butane sulphonic acid-(4-benzyl)piperazineamide**

The title product is obtained analogously to Example 8 from BOC-SO_2-Chatin-(4-Benzyl)-piperazine and BOC-Phe-Nle-OH. $[\alpha]_D^{20}$ = -25.6° (c = 0.32 in ethanol).

The starting compound BOC-SO_2-Chatin-(4-Benzyl)piperazine is obtained analogously to Example 1 from BOC-cyclohexylalaninale and 4-Benzyl-2-methylsulphonylpiperazine. The Starting compound 4-benzyl-1-methyl sulphonylpiperazine is prepared analogously to processes described in the literature reacting N-benzylpiperazine with Methansulphonylchloride in presence of pyridine in acetonitrile at -10° to 30°C.

Example 41: **(2R,3S)-3-(N-BOC-phenylalanyl-norleucyl)amido-4-cyclohexyl-2-hydroxy-butane-sulphonic acid-piperazineamide**

To a solution of 110 mg BOC-Phe-Nle-SO_2-Chatin-(4-benzyl)-piperazine (the compound of Example 40) in 120 ml glacial acetic acid, 20 mg of a 10% palladium on charcoal-catalyst are added. The mixture is hydrogenated during 6 hours at roomtemperature and at atmospheric pressure. The reaction mixture is filtrated over hyflo and the filtrate evaporated to dryness. The residue is dissolved in an ice-water-mixture, made slightly alkaline with a 10% aqueous sodiumcarbonate solution, extracted with methylenechloride, dried over sodiumsulphate, filtered and evaporated to dryness.

Chromatography on silicagel using methylene chloride containing 10% of ethanol as eluent yields the title product $[\alpha]_D^{20} = -22.5°$ (c = 0.2 in ethanol).

Example 42: **(2R,3S)-3-(N-BOC-Phenylalanyl-norleucyl)-amido-4-cyclohexyl-2-hydroxy-butane-sulphonic acid-(4-acetyl)piperazineamide**

The title product is obtained analogously to Example 8 by reacting BOC-SO_2-Chatin-(4-acetyl)-piperazine with BOC-Phe-Nle-OH. $[\alpha]_D^{20}$ = -19.5° (c = 0.21 in ethanol).

The starting compound BOC-SO_2-Chatin-(4-Acetyl)-piperazine is obtained by hydrogenating analogously to Example 41 BOC-SO_2-Chatin-(4-benzyl)piperazine (see Example 40) and reaction of the obtained BOC-SO_2-Chatin piperazine analogously to processes desribed in the literature with acetylchloride in presence of triethylamine in methylene chloride at 0°C.

Example 43: **(2R,3S)-3-(N-BOC-phenylalanyl-norleucyl)amido-4-cyclohexyl-2-hydroxy-butane-sulphonic acid-[4-(2,5,8,11-tetraoxadodecanyl)carbonyl] piperazineamide**

The title product is obtained reacting analogously to Example 8 BOC-SO_2-Chatin-(4-[2,5,8,11-tetraoxadodecanyl]carbonyl)-piperazine with BOC-Phe-Nle-OH. $[\alpha]_D^{20}$ = -16.7° (c = 0.12 in ethanol).

The starting product BOC-SO_2Chatin-(4-[2,5,8,11-Tetraoxa-dodecanyl]-carbonyl)piperazine is obtained in a manner known per se reacting 500 mg BOC-SO_2-Chatin-piperazine (see Example 42) with 260 mg 2,5,8,11-tetraoxadodecanylcarbonic acid in presence of 240 mg dicyclohexylcarbodiimide and 320 mg hydroxybenzotriazole in 10 ml N,N-Dimethylformamide.

Example 44: (2R,3S)-3-(N-BOC-Phenylalanyl-norleucyl)-amido -4-cyclohexyl-2-hydroxy-butane sulphonic acid-(4-methyl)piperazineamide

The title product is obtained analogously to Example 8 reacting BOC-SO_2-Chatin(4-Methyl)-piperazine with BOC-Phe-Nle-OH. $[\alpha]_D^{20}$ = -25.0° (c = 0.44 in Ethanol).

BOC-SO_2-Chatin-(4-Methyl)-piperazine is obtained analogously to Example 1 from BOC-Cyclohexylalaninal and 4-methyl-1-(methyl-sulphonyl)piperazine.

Example 45: (2R,3S)-3-(N-BOC-phenylalanyl-norleucyl)amido-4-cyclohexyl-2-hydroxy-butane-sulphonic acid-morpholineamide

The title product is obtained analogously to Example 8 by reacting BOC-SO_2-Chatin-morpholid with BOC-Phe-Nle-OH. $[\alpha]_D^{20}$ = -31.9° (c = 0.87 in Ethanol).

BOC-SO_2-Chatin-morpholid is obtained analogously to Example 1 from BOC-cyclohexylalaninal and morpholine.

Example 46: (2R,3S)-3-(N-BOC-Phenylalanyl-histidyl)amido-4-cyclohexyl-2-hydroxy-butane-sulphonic acid-piperidineamide

The title product is obtained analogously to Example 12 reacting BOC-SO_2-Chatin-piperidine (see Example 39) with BOC-Phe-His-OH. $[\alpha]_D^{20}$ = -14.1° (c = 0.17 in Pyridine).

Example 47: **(2R,3S)-3-(N-BOC-Phenylalanyl-norleucyl)amido-2-hydroxy-5-methylmercapto-pentane-sulphonic acid dimethylamide**

The title product is obtained analogously to Example 8 reacting BOC-SO_2-mettin-NMe_2 with BOC-Phe-Nle-OH. $[\alpha]_D^{20}$ = -31.0° (c = 0.67 in Ethanol).

BOC-SO_2-mettin-NMe_2 is prepared analogously to Example 1 from BOC-methioninal and methansulphonic acid dimethylamide.

Example 48: **(2R,3S)-3-(N-BOC-Phenylalanyl-norleucyl)amido-2-hydroxy-5-methylsulfinyl-pentane-sulphonic acid dimethylamide.**

To a solution of 50 mg BOC-Phe-Nle-SO_2-mettin-NMe_2(title product of Example 47) in 0,25 ml glacial acetic acid is added under stirring at 10° 0.01 ml of a 30% hydrogenperoxide-solution and the obtained mixture is stirred for additional 40 minutes at 10°C. The mixture subsequently evaporated to dryness and the residue is chromatographed on silicagel using methylenechloride containing 7% ethanol as eluent. The obtained title product is an environ 1 to 1 mixture of diastereomeres M.P.: Sinters from 82° on.

Example 49: **(2R,3S)-3-(N-BOC-Phenylalanyl-norleucyl)amido-2-hydroxy-4-benzylmercapto-butane-sulphonic acid dimethylamide**

The title product is obtained analogously to Example 8 reacting BOC-CYS (BZL) (OH)$CH_2SO_2NMe_2$ with BOC-Phe-Nle-OH.
$[\alpha]_D^{20}$ = -32.0° (c = 0.40 in Ethanol).

BOC-CYC(BZL) $(OH)CH_2SO_2NMe_2$ is obtained analogously to Example 1 by reacting BOC-S-Benzyl-L-cysteinal with methansulphonic acid dimethylamide.

BOC-S-Benzyl-L-cysteinal is prepared analogously to processes described in the literature reacting BOC-5-benzyl-L-cystein with 3,5-Dimethylpyrazol in chloroform in presence of dicyclohexyl carbodiimid and reduction of the obtained BOC-5-benzyl-L-cystein-3,5-dimethylpyrazolid with diisobutylaluminiumhydride in toluene.

Example 50: **(2R,3R)-3-(N-BOC-Phenylalanyl-norleucyl)amido 2-hydroxy-4-mercapto-butane-sulphonic acid dimethylamide**

To a solution of 300 mg BOC-Phe-Nle-CYS $(BZL)(OH)CH_2SO_2NMe_2$ (title product of Example 49) in 8 ml tetrahydrofurane and 20 ml liquid ammonia are added at -40° in portions 60 mg sodium. The blue coloured reaction mixture is stirred during additional 15 minutes at -40°, subsequently ammonium chloride is added in portions until the blue coloration disappears.The reaction mixture is evaporated to dryness, the residue is taken up in water and extracted with ethylacetate. The organic phase is washed with water and saturated aqueous sodium chloride solution, dried over sodium sulphate, filtered and evaporated to dryness. The residue is chromatographed on silicagel using methylene-chloride, containing 2% ethanol, as eluent. The resulting title product has an $[\alpha]_D^{20} = -33.6°$ (c = 0.3 in ethanol).

Example 51: **(2R,3R)-3-(N-BOC-Phenylalanyl-norleucyl)amido 2-hydroxy-4-ethylmercapto-butane-sulphonic acid-dimethylamide**

To a solution of 300 mg BOC-Phe-Nle-Cys (BZL)(OH)$CH_2SO_2NMe_2$ (title product of Example 49) in 8 ml tetrahydrofurane and 20 ml liquid ammonia are added, as described in Example 50, sodium and subsequently ammoniumchloride. After addition of ammoniumchloride at -40°C a solution of 0,05 ml ethylbromide in 2 ml tetrahydrofurane is added. The reaction mixture is stirred for further 10 minutes at -40° and subsequently, as desribed in Example 50, worked up and purified. It results the title product
$[\alpha]_D^{20}$ = -37.2° (c = 0.36 in ethanol).

Example 52: **(2R,3S)-3-[N-(2,3,4,6-tetra-O-acetyl-β- D-glucosyl-1-O]-isobutyrylphenylalanyl-norleucyl]amido-4-cyclohexyl-2-hydroxy-butane-sulphonic acid dimethylamide.**

The title product is obtained analogously to Example 8 reacting BOC-Phe-Nle-SO_2-Chatin-NMe_2 (title product of Example 10) with (2,3,4,6-tetra-O-acetyl-β-D-glycosyl-1-O-)isobutyric acid. $[\alpha]_D^{20}$ = -39.2° (c = 0.68 in ethanol).

(2,3,4,6-tetra-O-acetyl-β-D-glucosyl-1-O)isobutyric acid is obtained analogously to precessess described in the literature by condensation of α-D-acetobromoglucose with 2-hydroxy-2-methyl propionic acid benzyl ester and subsequent hydrogenation using 10% palladium on charcoal as catalyst.

Example 53: **(2R,3S)-3-[N-(β-D-glucosyl-1-0)-isobutyryl-phenyl alanyl-norleucyl]amido-4-cyclohexyl-2-hydroxy-butane-sulphonic acid dimethylamide**

To a solution of 150 mg (2,3,4,6-tetra-0-acetyl-β-D-glucosyl-1-0)isobutyryl-Phe-Nle-SO_2-Chatin-NMe_2 (title product of Example 52) in 5 ml methanol is added at room temperature a solution of 34 mg sodium in 1,5 ml methanol. The reaction-mixture is stirred for 30 minutes at room temperature, neutralised with 100 mg of the acidic ion exchanger Amberlyst 15, filtered and evaporated to dryness. The residue is chromatographed on silicagel using methylenechloride, containing 10% of ethanol, as eluent. The resulting title product has an $[\alpha]_D^{20} = -41.6°$ (c = 0.30 in ethanol).

Example 54: **(2S,3S)-3-(N-BOC-phenylalaninyl-histidyl)amido-1-(n-butylcarbamoylamino)-4-cyclohexyl-2-butanol**

402 mg of BOC-Phe-His-OH, 332 mg of (2S,3S)-3-amino-1-(n-butyl-carbamoylamino)-4-cyclohexyl-2-butanol-hydrochloride (intermediate product 8A) and 0.28 ml of triethylamine in 6.7 ml of dimethyl formamide are mixed with 0.23 ml of diphenylphosphoryl azide whilst cooling with ice. The mixture is stirred for 19 hours at room temperature and is concentrated by evaporation under a high vacuum. The residue is taken up in ethyl acetate and is washed in succession with aqueous tartaric acid, saturated sodium hydrogen carbonate solution and brine, then dried over anhydrous sodium sulphate and concentrated by evaporation. Chromatography of the residue (silica gel, 4 bar, methylene chloride-ethanol 19:1) yields the title compound, m.p. 141-2°C, $[\alpha]_D^{20} = -11.8°$ (c = 1 in methanol).

Example 55: **(2R,3S)-3-(N-BOC-phenylalaninyl-histidyl)amido-1-(n-butylcarbamoylamino)-4-cyclohexyl-2-butanol**

The title compound is obtained analogously to Example 54, using (2R,3S)-3-amino-1-(n-butylcarbamoylamino)-4-cyclohexyl-2-butanol-hydrochloride (8B), m.p. 148-9°C, $[\alpha]D^{20}$ = -14.5° (c = 1 in methanol).

Intermediate products 8A and 8B used in Examples 54 and 55 may be produced as follows:

a) (3S)-3-BOC-amido-4-cyclohexyl-1-nitro-2-butanone

(intermediate product 1D)

A solution of 32.6 ml of nitromethane in 160 ml of tetrahydrofuran, and 160 ml of hexamethylphosphoric acid triamide are added with vigorous stirring, whilst cooling with ice, to a suspension of 18.0 g of sodium hydride (80% in mineral oil) in 180 ml of tetrahydrofuran. The solution obtained is stirred for 1 hour at room temperature, then cooled to 0°, and a solution of 69.9 g of N-BOC-β-cyclohexyl-alanine-3,5-dimethylpyrazolide in 700 ml of tetrahydrofuran is added. After stirring for 20 hours, the mixture is mixed with 600 ml of 1N hydrochloric acid, extracted twice with ether, the combined organic extracts are washed with aqueous sodium chloride solution, dried over anhydrous sodium sulphate and evaporated under vacuum. The crude product is chromatographed on silica gel using toluene/ethyl acetate (6:1) as the eluant to produce the above intermediate product 1D as colourless crystals having a m.p. of 97-98°C.

b) (2S,3R)- and (2R,3S)-3-BOC-amino-4-cyclohexyl-1-nitro-2-butanol (intermediate products 9A and 9B)

2.27 g of sodium borohydride are added in small portions to an ice-cooled solution of 18.9 g of the above-obtained intermediate product 1D in 190 ml of ethanol. Then, stirring is effected for one hour without cooling, after which the pH value of the solution is adjusted to 3 by adding 10% aqueous tartaric acid and cooling. The solution is evaporated under vacuum, extracted twice with ether, the combined organic phases are washed with aqueous sodium chloride solution, dried over anhydrous sodium sulphate and evaporated under vacuum. Treatment of the remaining oily mixture of two diastereoisomers with ether/hexane yields isomer 9B with a m.p. of 116-118° (decomp.). Chromatography of the mother solution on silica gel using hexane/ether (2:1) as the eluant yields isomer 9A as an oil.
Rf values (silica gel, hexane/ether 2:1): 9A, 0.136; 9B, 0.106.

c) (2S,3S)- and (2R,3S)-1-amino-3-BOC-amino-4-cyclohexyl-2-butanol (intermediate products 10A and 10B)

5.96 g of ammonium formate are added in small portions over the course of 1 hour, in an inert atmosphere, to a mixture of 7.5 g of intermediate product 9A, which was obtained as described above, and 0.75 g of palladium (10% on animal charcoal) in 50 ml of methanol. After stirring for 17 hours at room temperature, the suspension is filtered through celite and the filtrate is evaporated under vacuum. The residue is taken up in 2N hydrochloric acid, washed twice with ether and the aqueous phase is rendered alkaline by adding sodium bicarbonate. The aqueous phase is extracted

twice with ethyl acetate, the organic phases are combined, dried over anhydrous sodium sulphate and evaporated under vacuum. The foamy residue is converted into the hydrogen oxalate and crystallised from ether. The hydrogen oxalate of intermediate product 10A is obtained, with a m.p. of 165-166° (decomp.).

The hydrogen oxalate of intermediate product 10B, which is obtained analogously from intermediate compound 9B, melts at 137-138°C (decomp.).

d) (2S,3S)-3-BOC-amino-1-(n-butylcarbamoyl)amino-4-cyclohexyl-2-butanol (intermediate product 11A)

A solution of 1.15 g of intermediate product 10A (free base) in 5 ml of anhydrous tetrahydrofuran is mixed with 0.45 ml of n-butylisocyanate whilst cooling with ice, stirred for 1 hour at room temperature and evaporated under vacuum. The residue is taken up in ethyl acetate, washed successively with 0.25 N hydrochloric acid, saturated sodium hydrogen carbonate solution and sodium chloride solution, dried over sodium sulphate and concentrated by evaporation. The title compound is obained as a crude foam.

(2R,3S)-3-BOC-amino-1-(n-butylcarbamoyl)amino-4-cyclohexyl-2-butanol (intermediate product 11B) is obtained analogously as a crude foam from intermediate product 10B.

e) (2S,3S)-3-amino-1-(n-butylcarbamoyl)amino-4-cyclohexyl-2-butanol-hydrochloride (intermediate product 8A)

1.39 g of the crude intermediate product 11A are stirred for

1 hour at room temperature in 14 ml of glacial acetic acid/conc. hydrochloric acid (9:1), and concentrated by evaporation under a high vacuum. The residue is taken up twice respectively in toluene and again evaporated to dryness. The title compound is obtained as an amorphous foam.

(2R,3S)-3-amino-1-(n-butylcarbamoyl)amino-4-cyclohexyl-2-butanol-hydrochloride (intermediate product 8B) is obtained analogously as an amorphous residue from intermediate product 11B.

Example 56: **(2S,3S)-3-(N-BOC-phenylalaninyl-norleucyl)amido-1-(isopropylcarbamoyl)amino-4-cyclohexyl-2-butanol**

A solution of 273 mg of (2S,3S)-1-amino-3-(N-BOC-phenylalaninyl-norleucyl)-amido-4-cyclohexyl-2-butanol (intermediate product 12A) in 10 ml of anhydrous tetrahydrofuran is mixed at 0° with 0.055 ml of isopropylisocyanate, stirred for 1 hour at room temperature and concentrated by evaporation under a high vacuum. Crystallisation of the residue from methylene chloride/methanol/hexane yields the title compound, m.p. 167-8°C (decomp.), $[\alpha]D^{20} = -16.2°$ (c = 1 in methanol).

Intermediate product 12A used in this example may be produced as follows:

a) (2S,3S)- and (2R,3S)-3-BOC-amino-1- CBZ - amino-4-cyclohexyl-2-butanol (intermediate products 13A and 13B)

4.18 ml of benzyl chloroformiate are added at a temperature of 2 to 5° to a solution of 5.28 ml of triethylamine and 6.3 g of inermediate compound 10A, which was obtained by the process in Example 55, in 120 ml of dichloromethane, and the

solution obtained is stirred for 30 minutes at room temperature. It is then diluted with dichloromethane and washed with 0.25N hydrochloric acid, saturated aqueous sodium bicarbonate solution and water. The organic phase is dried over sodium sulphate and evaporated under vacuum. Chromatography of the residue on silica gel, using toluene-ethyl acetate (3:1) as the eluant yields intermediate product 13A as a slightly yellowish oil.

Intermediate product 13B is obtained as an oil from intermediate product 10B, using the same process.

b) (2S,3S)- and (2R,3S)-3-amino-1-CBZ-amino-4-cyclohexyl-2-butanol (intermediate products 14A and 14B)

8.06 g of intermediate product 13A are added whilst cooling to 80 ml of the mixture of acetic acid/conc. hydrochloric acid (9:1), and the solution obtained is stirred for 1 hour at room temperature and is then evaporated to dryness. The hydrochloride of intermediate product 14A is thus obtained as a colourless foam.

The hydrochloride of intermediate product 14B is obtained from intermediate product 13B using the same process.

c) (2S,3S)- and (2R,3S)-3-(BOC-phenylalaninyl-norleucinyl) amino-1-CBZ-amino-4-cyclohexyl-2-butanol (intermediate products 15A and 15B)

4.06 ml of diphenylphosphoryl azide and 4.94 ml of triethylamine are gradually added to an ice-cooled solution of 6.68 g of BOC-Phe-Nle-OH and 6.3 g of crude hydrochloride of

intermediate product 14A in dimethylformamide, and the clear solution obtained is stirred over night at room temperature, then concentrated under vacuum, taken up in dichloromethane, and the dichloromethane solution is washed with 0.25N hydrochloric acid, saturated aqueous sodium bicarbonate solution and water, and dried over anhydrous sodium sulphate. After evaporation under vacuum, the residue is chromatographed on silica gel (dichloromethane/ethanol 49:1 as the eluant) and the product obtained is crystallised from dichloromethane/-hexane. Intermediate product 15A thus obtained melts at 167-168°C (decomp.).

Intermediate product 15B with a m.p. of 150-151° (decomp.) is obtained from intermediate product 14B, using the same process.

d) (2S,3S)- and (2R,3S)-1-amino-3-(BOC-phenylalaninyl-norleucyl)-amino-4-cyclohexyl-2-butanol (intermediate products 16A and 16B)

7.0 g of intermediate product 15A and 0.7 g of palladium on active charcoal (10%) in 140 ml of methanol are hydrogenated for 1½ hours at room temperature in a hydrogen atmosphere at atmospheric pressure, subsequently diluted with dichloromethane and filtered through celite. After evaporation of the filtrate under vacuum and crystallisation of the residue from methanol/ether, intermediate product 16A is obtained as colourless crystals having a m.p. of 140-141°, $[\alpha]_D^{20} = -38.5°$ (c = 1 in methanol).

Intermediate product 16B is obtained as colourless crystals having a m.p. of 168-169° (decomp.) from intermediate product

15B, using the same process. $[\alpha]_D^{20}$ = -25.6° (c = 1 in methanol).

Example 57: **(2S,3S)-3-[N-(3-cyclohexylpropionyl)-norleucyl] amido-1-(isopropylcarbamoyl)amino-4-cyclohexyl-2-butanol**

A solution of 135 mg of N-(3-cyclohexylpropionyl)norleucine, 154 mg of (2S,3S)-3-amino-1-(isopropylcarbamoyl)amino-2-butanol-hydrochloride and 150 ml of 1-hydroxybenzotriazole in 2.6 ml of dimethylformamide is mixed at 0°C with 104 mg of N,N'-dicyclohexylcarbodiimide and 0.07 ml of triethylamine, stirred for 1 hour at 0°, then for 15 hours at room temperature, cooled again to 0°C, and the resultant dicyclohexylurea is filtered off. The filtrate is evaporated under a high vacuum, the residue taken up in methylene chloride and washed successively with 0.25N hydrochloric acid, saturated sodium hydrogen carbonate solution and water. The organic phase is dried over sodium sulphate and concentrated by evaporation. Chromatography of the residue (silica gel, 6 bar, methylene chloride-ethanol 19:1) yields the amorphous title compound, $[\alpha]_D^{20}$ = -18.0° (c = 1 in methanol).

The intermediate products used in Example 57 may be produced as follows:

a) N-3-cyclohexylpropionyl-norleucine

A solution of 1.31 g of L-norleucine in 22 ml of ether and 22 ml of 1N sodium hydroxide is mixed at 0° with 1.92 g of 3-cyclohexylpropionic acid chloride, stirred for 1 hour at 0°C, then acidified with 0.25N hydrochloric acid and twice extracted with ether. The combined organic phases are washed

with saturated sodium chloride solution, dried over sodium sulphate and concentrated by evaporation. Crystallisation of the residue from ether/hexane yields the title compound, m.p. 138-9°C (decomp.).

b) (2S,3S)-3-amino-1-(isopropylcarbamoyl)amino-4-cyclohexyl-2-butanol-HCl

(2S,3S)-3-BOC-amino-1-(isopropylcarbamoyl)amino-4-cyclohexyl-2-butanol is obtained analogously to Example 55 d), using intermediate product 10A and isopropylisocyanate. The BOC-protecting group is cleaved from the product obtained analogously to Example 55 e), and the amorphous title compound is thus obtained.

Example 58: (2S,3S)-3-(N-BOC-phenylalaninyl-norleucyl)amido-1-[bis-(dimethylamino)]phosphorylamido-4-cyclohexyl-2-butanol

A solution of 273 mg of (2S,3S)-3-(N-BOC-phenylalaninyl-norleucyl)-amido-1-amino-4-cyclohexyl-2-butanol (intermediate product 16A, see Example 56 d)) and 0.07 ml of triethylamine in 3.4 ml of anhydrous tetrahydrofuran is mixed at 0°C with a solution of 0.076 ml of phosphoric acid-bis(dimethylamide)-chloride in 3.4 ml of anhydrous tetrahydrofuran. The resultant suspension is mixed at room temperature with a further 6,8 ml of tetrahydrofurane and 3.4 ml of hexamethylphosphoric acid triamide and a spatula tip of 4-dimethylaminopyridine, and the clear solution is stirred for 5 days at room temperature. The solution is subsequently concentrated under a high vacuum, the residue is taken up in ethyl acetate, washed successively with ice-cold 0.25N hydrochloric acid, saturated sodium hydrogen carbonate solution

and sodium chloride solution, dried over sodium sulphate and concentrated by evaporation. Crystallisation of the residue from methylene chloride/hexane yields the title compound m.p. 171-2°C (decomp.), $[\alpha]D^{20}$ = -27.7° (c = 1 in chloroform).

Example 59: **(2S,3S)-3-(N-BOC-phenylalaninyl-norleucyl)-1-(N-benzyl-4-piperidinocarbamoyl)amino-4-cyclohexyl-2-butanol**

The title compound is obtained analogously to Example 56, using N-benzyl-4-piperidino-isocyanate instead of isopropylisocyanate, m.p. 166-8°C, $[\alpha]_D^{20}$ = -13.5° (c = 1 in methanol).

Example 60: **(2S,3S)-3-(N-BOC-phenylalaninyl-norleucyl)amido-1-(4-piperidinocarbamoyl)amino-4-cyclohexyl-2-butanol**

200 mg of the title compound of Example 59 in 20 ml of methanol are hydrogenated for 20 hours at room temperature in a hydrogen atomosphere in the presence of palladium (10% on active charcoal), then the suspension is filtered through celite and the filtrate is concentrated by evaporation. Crystallisation of the residue with methanol-ether yields the title compound, m.p. 173-5°, $[\alpha]_D^{20}$ = -15.5° (c = 1 in methanol).

Example 61: **(2S,3S)-3-(N-BOC-phenylalaninyl-norleucyl)amido-1-(dimethyl-carbamoyl)amino-4-cyclohexyl-2-butanol**

The title compound is obtained analogously to Example 56, using dimethylcarbamoyl chloride and triethylamine instead of isobutyl-isocyanate, m.p. 157-8°C, $[\alpha]_D^{20}$ = -10.0° (c = 2 in methanol).

Example 62: **(2S,3S)-3-(N-BOC-phenylalaninyl-norleucyl)amido-1-(isopropyl-carbamoyl)-isopropylamino-4-cyclohexyl-2-butanol**

A solution of 189 mg of N-BOC-phenylalaninyl-norleucine, 172 mg of (2S,3S)-3-amino-1-(isopropylcarbamoyl)-isopropylamino-4-cyclohexyl-2-butanol (intermediate product 17) and 150 mg of 1-hydroxy-benzotriazole in 3.4 ml of dimethylformamide is mixed at 0°C with 99 mg of N-ethyl-N'-(3-dimethylamino-propyl)carbodiimide-hydrochloride and 0.07 ml of triethylamine, stirred for one hour at 0°C and for 20 hours at room temperature, and then concentrated in a rotary evaporator at 30°C. The residue is taken up in methylene chloride, washed successively with cold 0.25N hydrochloric acid, saturated sodium hydrogen carbonate solution and water, dried over sodium sulphate and concentrated by evaporation. Chromatography of the residue (silica gel, 5 bar, methylene chloride-ethanol) yields the title compound, $[\alpha]_D^{20} = -5.0°$ (c = 1 in methanol).

Intermediate product 17 used in this example may be produced as follows:

a) (2S,3S)-3-N-BOC-amino-1-isopropylamino-4-cyclohexyl-2-butanol

A mixture of 3.26 g of intermediate product 10A (see Example 55c), 1.59 g of sodium carbonate and 1.02 ml of isopropyl iodide in 30 ml of tetrahydrofuran is refluxed for 16 hours, then the cooled suspension is filtered and the filtrate concentrated by evaporation. Chromatography of the residue (silica gel, 4 bar, methylene chloride/methanol/conc. ammonia 90:9:1) yields the title compound (amorph.).

b) (2S,3S)-3-N-BOC-amino-1-(isopropylcarbamoyl)-isopropyl-amino-4-cyclohexyl-2-butanol

A solution of 591 mg of the above product in 6 ml of tetrahydrofuran is mixed at 0° with 0.2 ml of isopropylisocyanate, stirred for 20 hours at room temperature and then concentrated by evaporation. Chromatography (silica gel, 5 bar, methylene chloride-ethanol 19:1)yields the amorphous title compound.

Example 63: (2S,3S)-3-[N-(1-adamantyl-propionyl)-norleucyl]-1-ispropylcarbamoyl)amino-4-cyclohexyl-2-butanol

The title compound is obtained analogously to Example 57, using N-(1-adamantyl-propionyl)norleucine instead of N-(3-cyclohexyl-propionyl)norleucine, m.p. 230-1°C $[\alpha]_D^{20}$ = -24.5° (c = 1 in dimethylformamide)-

Example 64: (2S,3S)-3-(N-BOC-norleucyl)-amido-1-(isopropyl-carbamoyl)amino-4-cyclohexyl-2-butanol

The title compound is obtained analogously to Example 57, using N-BOC-norleucine instead of N-(3-cyclohexylpropionyl)norleucine, m.p. 225-6°C (decomp.).

Example 65: (2S,3S)-3-(norleucyl)amido-1-(isopropylcarbamoyl)-amino-4-cyclohexyl-2-butanol-hydrochloride

339 mg of the product of Example 64 are treated with 3.4 ml of glacial acetic acid/conc. hydrochloric acid and worked up,

analogously to Example 55e. The title compound is obtained as a colourless foam.

Example 66: **(2S,3S)-3-N-[1-benzoyl-amino-2-(1-naphthyl) propenoyl-norleucyl]amino-4-cyclohexyl-1-(isopropyl-amino-carbamoyl)amino-2-butanol**

A solution of 168 mg of the product of Example 65, 120 mg of 5-(1-naphthyl-methylidene)-2-phenyl-4-oxazolone (azalactone of 1-naphthaldehyde and N-benzoylglycine) and 0.056 ml of triethyl-amine in 2.7 ml of chloroform is mixed with a spatula tip of 4-dimethylaminopyridine, refluxed for 4 hours and subsequently concentrated by evaporation. Chromatography of the residue (silica gel, 6 bar, ethyl acetate) yields the amorphous title compound, $[\alpha]_D^{20} = -58.2°$ (c = 1 in methanol).

Example 67: **(2S,3S)-3-[N-(bis(1-naphthyl-methyl)acetyl) norleucyl]amino-4-cyclohexyl-1-(isopropylcarbamoyl)-amino-2-butanol**

The title compound is obtained analogously to example 57, using N-(bis(1-naphthyl-methyl)acetyl)norleucine instead of N-(3-cyclo-hexylpropionyl)-norleucine, m.p. 173-4°, $[\alpha]_D^{20} = -52.0°$ (c = 1 in methanol).

Example 68: **(2S,3S)-3-(N-cyclopentyl-carbonyl-phenylalaninyl)-norleucyl)amino-4-cyclohexyl-1-(isopropyl-carbamoyl)-amino-2-butanol**

Coupling of N-cyclopentylcarbonyl-phenylalanine and (2S,3S)-3-(norleucyl)amido-1-(isopropylcarbamoyl)amino-4-cyclohexyl-2-

butanol-hydrochloride (Example 65) analogously to Example 57 yields the title compound, m.p. 213-5°C (decomp.), $[\alpha]_D^{20}$ = -18.2° (c = 0.5 in methanol).

Example 69: **(2S,3S)-3-(N-BOC-phenylalaninyl-histidyl)amido-1-(isopropyl-carbamoyl)amino-4-cyclohexyl-2-butanol**

The title compound is obtained as an amorphous powder, analogously to Example 57, using N-BOC-phenylalaninyl-histidine instead of N-(3-cyclohexylpropionyl)norleucine, $[\alpha]_D^{20}$ = -10.8° (c = 1 in methanol).

ABBREVIATIONS:

In the preceding Examples the following abbreviations were used:

SO_2Adatin	(2R,3S)-4-(1-Adamantyl)-3-amino-2-hydroxy-butanesulphonic acid
SO_2Chatin	(2R,3S)-3-Amino-4-cyclohexyl-2-hydroxy-butanesulphonic acid
SO_2Sta	(2R,3S)-3-Amino-2-hydroxy-5-methyl-hexanesulphonic acid
SO_2-Aminochatin	(2R,3S)-2,3-Diamino-4-cyclohexyl-butanesulphonic acid
SO_2-Desoxychatin	(3S)-3-Amino-4-cyclohexyl-butanesulphonic acid

SO_2-Dioxolan	(2R,3S)-3-Amino-4-(1,4-dioxaspiro[4,5]undec-8-yl)-2-hydroxybutanesulphonic acid
SO_2-onChatin	(2R,3S)-3-Amino-4-(2'-oxocyclohexyl)-2-hydroxy-butanesulphonic acid
SO_2-olChatin	(2R,3S)-3-Amino-4-(4'hydroxycyclohexyl)-2-hydroxy-butanesulphonic acid
SO_2(2-Naphthin)	(2R,3S)-3-Amino-2-hydroxy-4-(2-naphthyl)-butanesulphonic acid
SO_2Neotin	(2R,4S)-3-Amino-5,5-dimethyl-2-hydroxy-hexanesulphonic acid
Achps	(3S,4S)-4-Amino-5-cyclohexyl-3-hydroxy-pentane-sulphonic acid
Achips	(1S,3S,4S)-4-Amino-5-cyclohexyl-3-hydroxy-1-isopropyl-pentanesulphonic acid
SO_2-Mettin	(2R,3S)-3-Amino-5-methylmercapto-2-hydroxy-pentanesulphonic acid
SO_2-Mettin(O)	(2R,3S)-3-Amino-5-methylsulfinyl-2-hydroxypentanesulphonic acid
Cys(BZL)(OH)CH_2SO_2	(2R,3R)-3-Amino-4-benzylmercapto-2-hydroxy-butanesulphonic acid
Cys(Et)(OH)CH_2SO_2	(2R,3R)-3-Amino-4-ethylmercapto-2-hydroxy-butanesulphonic acid

$Cys(OH)CH_2SO_2$ (2R,3R)-3-Amino-4-mercapto-2-hydroxybutane-sulphonic acid

The compounds according to the invention have pharmacological activity. They can be used as medicaments.

As can be deduced from standard tests, they have effects which are typical in particular for enzyme inhibitors. The inhibiting activity in relation to a specific enzyme depends of course on the peptide structure as a whole. The above compunds which are suitable in particular as inhibitors of renin activity, when used on human synthetic tetradecapeptide substrate at a concentration of 10^{-5}M to 10^{-11}M, effect a 50% inhibition of enzyme activity of pure human renin according to the method of F. Cumin et al. (Bioch. Biophys. Acta 913, 10-19 (1987)).

In the "antibody-trapping" method of K. Poulsen and J. Jorgensen (J. Clin. Endocrin. Metab. 39 [1974] 816-825), they inhibit human plasma renin activity at a concentration of 10^{-5}M to 10^{-11}M.

The title compounds of Examples 12, diastereorisomer A (lowest inhibiting concentration 0,17 nM/l highest inhibiting concentration 17 nM/l IC_{50} = 1,7 nM/L), 23 (lowest inhibiting concentration 0,75 nM/l, highest inhibiting concentration 75 nM/l, IC_{50} = 7,5 nM/l), 11 (lowest inhibiting concentration 0,75 nM/l, highest inhibiting concentration 75 nM/l, IC_{50} = 7,5 nM/l), 31 (lowest inhibiting concentration 0,8 nM/l, highest inhibiting concentration 80 nM/l; IC_{50} = 8,0 nM/l), 67 (lowest inhibiting concentration 1,1 nM/l, highest inhibiting concentration 110 nM/l; IC_{50} = 11 nM/l) and 54 (lowest inhibiting concentration 1,6 nM/l, highest inhibiting concentration 160 nM/l; IC_{50} = 16 nM/l) are preferred for the prophylaxis and treatment of hypertension and cardiac insufficiency.

The compounds according to the invention are therefore suitable for the propylaxis and treatment of conditions which are characterized by enzymatic malfunction, and for which an inhibition of enzymatic activity is indicated.

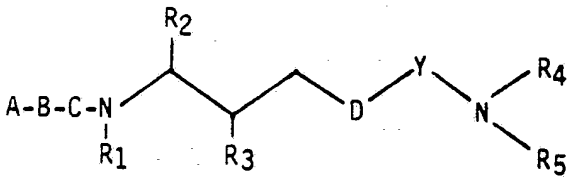
As renin inhibitors, they are suitable e.g. for use in the prophylaxis and treatment of hypertension and cardiac insufficiency ("congestive heart failure").

For above applications, the dosage to be administered depends on the compound respectively used, the type of administration and the desired treatment. In general, satisfactory results are obtained if the compounds are administered in a daily dosage of 0.02 mg/kg to ca. 10 mg/kg animal body weight. For larger mammals, the recommended daily dosage is from about 1 mg to about 500 mg, conveniently administered e.g. orally in doses of 0.25 mg to ca. 500 mg 1-4 times daily or in sustained release form.

The compounds according to the invention may be administered in free form, or if acidic or basic groups are present, in pharmacologically acceptable salt form. Such salt forms have the same order of activity as the free forms and can be produced in known manner. The present invention similarly relates to pharmaceutical preparations containing a compound according to the invention in free form or in pharmaceutically acceptable salt form, optionally together with pharmaceutically acceptable adjuvants and/or carriers. Such pharmaceutical preparations may be formulated for use in enteral, preferably oral administration, e.g. as teblets, or for use in parenteral administration, e.g. as injectable solutions or suspensions.

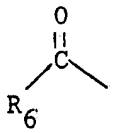
What we claim is:

1. Compounds of Formula I



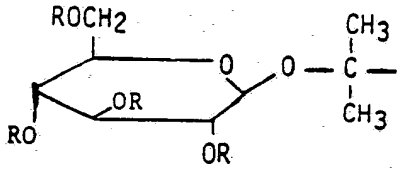
I

wherein

A signifies an acyl group of formula  wherein

R_6 denotes straight-chain or branched (C_{1-10})alkyl radical which may be optionally substituted by (C_{1-5})alkoxy or (C_6-C_{10})aryloxy; a (C_{3-7})cycloalkyl radical, a (C_{3-10})-cycloalkyl-(C_{1-5})alkyl radical, a (C_{6-10})aryl radical, a 5- or 6-membered heteroaryl radical containing one or two nitrogen atoms, oxygen or sulphur atoms or one nitrogen atom and one oxygen atom and/or one sulphur atom; or a heteroaryl- (C_{1-5})-alkyl radical wherein the heteroaryl moiety is 5- or 6-membered and contains one or two nitrogen atoms, oxygen or sulphur atoms or one nitrogen atom and one oxygen atom and/or one sulphur atom; a straight-chain or branched (C_{1-5})alkoxy radical or a (C_{6-10})aryl-(C_{1-5})-alkoxy radical or a group of formula $R_{10}O(CH_2CH_2O)_n(CH_2)_m$-, wherein R_{10} signifies a straight-chain or branched (C_{1-5})alkyl radical, n signifies

a whole number from 1 to 20 and m signifies a whole number from 1 to 5, or a group of Formula

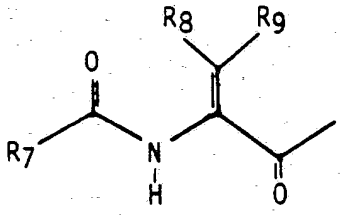


wherein

R signifies hydrogen or acetyl

or

A signifies a group of formula



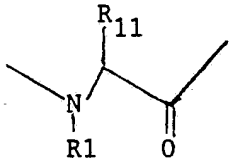
wherein

R_7 signifies a straight-chain or branched (C_{1-5})alkyl radical or a (C_{6-10})aryl radical and

R_8 and R_9 respectively denote hydrogen, a straight-chain or branched (C_{1-5})-alkyl radical or a (C_{6-10})aryl radical,

R_1 signifies hydrogen or a straight-chain or branched (C_{1-5})-alkyl radical,

B and C are the same or different and signify a bond or a group of formula



wherein

R_1 is defined as above and R_{11} signifies a hydrophilic or lipophilic amino acid side chain,

whereby

B and C cannot simultaneously signify a bond

D signifies a bond or denotes -O-, $-\underset{\underset{R_1}{|}}{N}-$ or $-\underset{\underset{R_1}{|}}{CH}-$

whereby R_1 is defined as mentioned above,

R_2 denotes a straight-chain or branched (C_{1-10})alkyl radical, a (C_{3-10})cycloalkyl(C_{1-5})alkyl radical which is optionally substituted in the cycloalkyl moiety, a (C_{6-10})aryl-(C_{1-5})-alkyl radical or a heteroaryl-(C1-5)-alkyl radical, wherein the heteroaryl moiety is 5- or 6-membered and contains one or two nitrogen atoms, oxygen or sulphur atoms or one nitrogen atom and one oxygen atom and/or one sulphur atom, or a group of formula

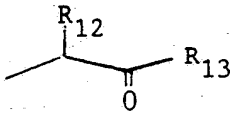
$$R_{15}-\overset{\overset{(O)_s}{\|}}{S}-(CH_2)p-$$

wherein

R_{15} signifies Hydrogen, (C_{1-4})alkyl or benzyl, s is 0 or 1 and p is 1 or 2,

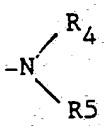
R_3 signifies hydrogen, a hydroxyl group, an amino group or a group of formula $-OCOR_2$, wherein R_2 is defined as above,

R_4 and R_5 are the same or different and respectively signify hydrogen, a straight-chain or branched (C_{1-5})alkyl radical, a (C_{6-10})-aryl-(C_{1-5})-alkyl or a heteroaryl-(C1-5)-alkyl radical, wherein the heteroaryl moiety is 5- or 6-membered and contains one or two nitrogen atoms, oxygen or sulphur atoms or one nitrogen atom and one oxygen atom and/or one sulphur atom,

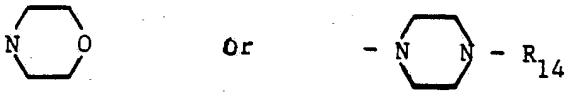
or it denotes a group of formula 

wherein R_{12} signifies a straight-chain or branched (C_{1-5})-alkyl radical or a straight-chain or branched (C_{1-5})-hydroxy-alkyl radical, R_{13} denotes a hydroxyl radical, a straight-chain or branched (C_{1-5})alkoxy group, an amino group or a (C_{1-5})alkylamino group, whereby the alkyl radical is straight-chain or branched, an aminomethylpyridyl group

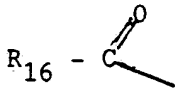
or a benzyl group, or

the radical 

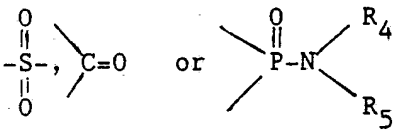
denotes groups of formulae



wherein R_{14} signifies hydrogen, (C_{1-5})-alkyl, benzyl, or a group of formula

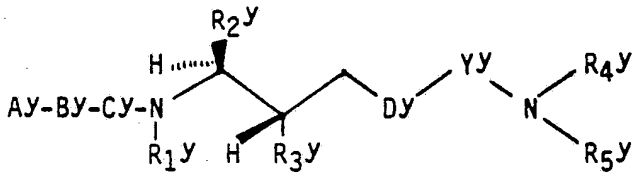


wherein R_{16} denotes (C_{1-4})Alkyl or (C_{1-4})alkoxy $(OC_2H_2)q-CH_2-$ wherein q signifies a whole number from 2 to 5.

Y signifies 

wherein R_4 and R_5 have the significances given above.

2. Compounds according to claim 1 of Formula



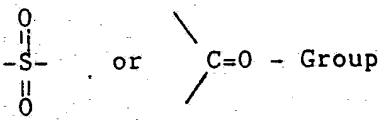
Iy

wherein

A^y signifies tert.-butyloxycarbonyl, pivaloyl, bis(1-naphthylmethyl)acetyl, benzoyl or 1-adamantylcarbonyl,

B^y signifies a bond, phenylalanine or β-cyclohexylalanine,

C^y signifies histidine, norleucine, phenylalanine or leucine,

Y^y signifies a  - Group

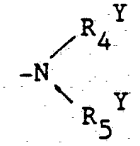
$R_1{}^y$ signifies hydrogen or methyl,

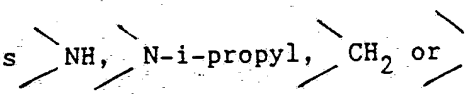
$R_2{}^y$ signifies isobutyl, benzyl, cyclohexylmethyl or 1-adamantylmethyl,

$R_3{}^y$ signifies hydroxy, amino or groups of formulae $OCOCH_3$ or $OCOC(CH_3)_3$,

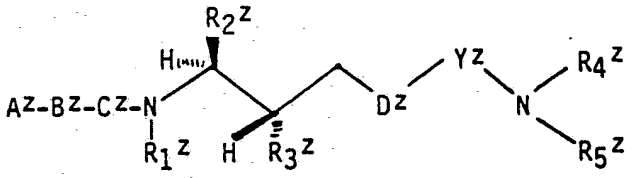
$R_4{}^y$ signifies hydrogen, methyl, i-propyl, i-butyl or n-butyl,

$R_5{}^y$ signifies methyl, i-propyl, i-butyl or n-butyl, or

the group  signifies a pyrrolidinyl-, piperidinyl or a morpholinyl-group and

D^y signifies  -groups.

3. Compounds according to claim 1 of Formula



Iz

wherein

A^z signifies tert.-butyloxycarbonyl or bis(1-naphthylmethyl)-acetyl,

B^z signifies a bond, phenylalaninyl or β-cyclohexylalaninyl,

C^z signifies histidine, leucine or norleucine,

Y^z signifies a $-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-$ or a $\diagdown\!\!\diagup C=O$-group

R_1^z signifies hydrogen,

R_2^z signifies cyclohexylmethyl or 1-adamantylmethyl,

R_3^z signifies hydroxy or amino,

R_4^z signifies hydrogen or methyl,

R_5^z signifies hydrogen, isopropyl or isobutyl or

The group $-N\begin{matrix}\diagup R_4^z \\ \diagdown R_5^z\end{matrix}$ signifies a pyrrolidinyl-, a piperidinyl or a morpholinyl-group and

D^z signifies $\diagdown$NH or $\diagdown$CH-isopropyl or $\diagdown$$CH_2$-groups.

4. A compound of claim 1 selected from

(2S,3S)-3-(N-BOC-Phenylalaninyl-histidyl)amido-1-(n-butylcarbomoyl-amino)-4-cyclohexyl-2-butanol

(2R,3S)-3-(N-BOC-Phenylalaninyl-histidyl)amido-1-(n-butylcarbamoyl-amino)-4-cyclohexyl-2-butanol

(2S,3S)-3-(N-BOC-Phenylalaninyl-norleucyl)amido-1-(iso-propylcarba-moyl)amino-4-cyclohexyl-2-butanol

(2S,3S)-3-[N-(3-Cyclohexylpropionyl)-norleucyl]amido-1-(isopropyl-carbamoyl)amino-4-cyclohexyl-2-butanol

(2S,3S)-3-(N-BOC-Phenylalaninyl-norleucyl)amido-1-[bis-(dimethyl-amino)]phosphorylamido-4-cyclohexyl-2-butanol

(2S,3S)-3-(N-BOC-Phenylalaninyl-norleucyl)-1-(N-benzyl-4-piperidino-carbamoyl)amino-4-cyclohexyl-2-butanol

(2S,3S)-3-(N-BOC-Phenylalaninyl-norleucyl)amido-1-(4-piperidino-carbamoyl)amino-4-cyclohexyl-2-butanol

(2S,3S)-3-(N-BOC-Phenylalaninyl-norleucyl)amido-1-(di-methyl-carbamoyl)amino-4-cyclohexyl-2-butanol

(2S,3S)-3-(N-BOC-Phenylalaninyl-norleucyl)amido-1-(iso-propyl-carbamoyl)-isopropylamino-4-cyclohexyl-2-butanol

(2S,3S)-3-[N-(1-Adamantyl-propionyl)-norleucyl]-1-(iso-propylcarbamoyl)amino-4-cyclohexyl-2-butanol

(2S,3S)-3-(N-BOC-Norleucyl)-amido-1-(isopropylcarbamoyl)amino-4-cyclohexyl-2-butanol

(2S,3S)-3-(Norleucyl)amido-1-(isopropylcarbamoyl)amino-4-cyclohexyl-2-butanol-hydrochloride

(2S,3S)-3- N-[1-Benzoyl-amino-2-(1-naphthyl)propenoyl-norleucyl]amino 4-cyclohexyl-1-(isopropylaminocarbamoyl)amino-2-butanol

(2S,3S)-3-[N-(Bis(1-Naphthyl-methyl)acetyl)-norleucyl]-amino-4-cyclohexyl-1-(isopropylcarbamoyl)amino-2-butanol

(2S,3S)-3-(N-Cyclopentyl-carbonyl-phenylalaninyl-norleucyl)amino-4-cyclohexyl-1-(isopropyl-carbamoyl)amino-2-butanol

(2S,3S)-3-(N-BOC-Phenylalaninyl-histidyl)amido-1-(isopropyl-carbamoyl) amino-4-cyclohexyl-2-butanol

(2R,3S)-3-(tert-Butyloxycarbonylamino)-4-cyclohexyl-2-hydroxybutanesulphonic acid dimethylamide

(2R,3S)-3-(tert-Butyloxycarbonylamino)-4-(1,4-dioxaspiro[4,5]undec-8-yl)-2-hydroxybutane-sulphonic acid dimethylamide

(2R,3S)-3-(tert-Butyloxycarbonylamino)-4-cyclohexyl-2-azido-butane-sulphonic acid dimethylamide

(2R,3S)-3-(tert-Butyloxycarbonylamino)-2-hydroxy-4-(2-naphthyl)-butane-sulphonic acid dimethylamide

(2R,3S)-3-(tert-Butyloxycarbonylamino)-2-hydroxy-5-methyl-hexane-sulphonic acid dimethylamide

((3S,4S)-4-(tert-Butyloxycarbonylamino)-5-cyclohexyl-3-hydroxy-pentane-sulphonic acid dimethylamide

(1S,3S,4S)-4-(tert-Butyloxycarbonylamino)-5-cyclohexyl-3-hydroxy-1-isopropyl-pentane-sulphonic acid dimethylamide

(2R,3S)-3-(N-BOC-Phenylalanyl-phenylalanyl)amido-4-cyclohexyl-2-hydroxy-butane sulphonic acid dimethylamide

(2R,3S)-3-(N-BOC-ß-Cyclohexylalanyl-ß-cyclohexylalanyl)amido-4-cyclohexyl-2-hydroxy-butane sulphonic acid dimethylamide

(2R,3S)-3-(N-BOC-Phenylalanyl-norleucyl)amido-4-cyclohexyl-2-hydroxy-butane sulphonic acid dimethylamide

(2R,3S)-3-(N-BOC-ß-Cyclohexylalanyl-norleucyl)amido-4-cyclohexyl-2-hydroxy-butane sulphonic acid dimethylamide

(2R,3S)-3-(N-BOC-Phenylalanyl-histidyl)amido-4-cyclohexyl-2-hydroxy-butane sulphonic acid dimethylamide

(2R,3S)-3-[N-(BIS-(1-Naphthylmethyl)acetyl)norleucyl]amido-4-cyclohexyl-2-hydroxy-butane sulphonic acid dimethylamide

(2R,3S)-3-(N-BOC-Phenylalanyl-norleucyl)amido-2-amino-4-cyclohexyl-butane sulphonic acid dimethylamide

(2R,3S)-3-(N-BOC-Phenylalanyl-norleucyl)amido-4-(1,4-dioxa-spiro[4.5]undec-8-yl)-2-hydroxy-butane sulphonic acid dimethylamide

(2R,3S)-3-(N-BOC-Phenylalanyl-norleucyl)amido-4-(4'-oxocyclo-hexyl)-2-hydroxy-butane sulphonic acid dimethylamide

(2R,3S)-3-(N-BOC-Phenylalanyl-norleucyl)amido-4-(4'-hydroxy-cyclohexyl)-2-hydroxy-butane sulphonic acid dimethylamide

(3S,4S)-3-(N-BOC-Phenylalanyl-norleucyl)amido-5-cyclo hexyl)-3-hydroxy- pentane sulfonic acid dimethylamide

(1R,3S,4S)-4-(N-BOC-Phenylalanyl-norleucyl)amido-5-cyclohexyl-3-hydroxy-isopropyl-pentane sulphonic acid dimethylamide

(2R,3S)-3-(N-BOC-Phenylalanyl-norleucyl)amido-2-hydroxy-4-(2-naphthyl)-butane sulphonic acid dimethylamide

(2R,3S)-3-[N-(BIS-(1-Naphthylmethyl)acetyl)-norleucyl] amido-2-hydroxy-5- methyl-hexane sulphonic acid dimethylamide

(2S,3S)- und (2R,3S)-3-(BOC-Phenylalanyl-norleucyl)-amido-4-cyclohexyl-1-isobutyl-sulfamoylamino-2-butanol

(2S,3S)-3-(BOC-Phenylalaninyl-norleucyl)amido-4-cyclohexyl-1-dimethylsulfamoylamino-2-butanol

(2R,3S)-3-(N-Benzoyl-dehydrophenylalaninyl-norleucyl)-amido-1-dimethylsulfamoyl-amino-5-methyl-2-hexanol

N-(3-Cyclohexylpropionyl)-norleucin

(2S,3S)-3-(3-Cyclohexyl-propionyl-norleucyl)amido-1-Cbz-amino-4-cyclohexyl-2-butanol

(2S,3S)-3-(3-Cyclohexyl-propionyl-norleucyl)amido-1-amino-4-cyclohexyl-2-butanol

(2S,3S)-3-(3-Cyclohexyl-propionyl-norleucyl)amido-4-cyclohexyl-1-dimethylsulfamoylamino-2-butanol

(2R,3S)-3-[N(1-Adamantyl)propionyl)norleucyl]amido-4-cyclohexyl-2-hydroxy-butane sulphonic acid dimethylamide

(2R,3S)-3-(N-BOC-ß-Cyclohexylalanylhistidyl)amido-4-cyclohexyl-2-hydroxy-butane sulphonic acid dimethylamide

(2R,3S)-3-[N-(BIS-(1-Naphthylmethyl)acetyl)histidyl]amido-4-cyclohexyl-2-hydroxy-butane sulphonic acid dimethylamide

(2R,3S)-3-[N-BOC-ß-(2,1,3-Benzoxadiazol-4-yl)alanyl-norleucyl]amido-4-cyclohexyl-2-hydroxy-butane sulphonic acid dimethylamide

(2R,3S)-3-((N-[2-Methoxy-poly(2-ethoxy)acetyl]phenylalanyl-norleucyl))amido-4-cyclohexyl-2-hydroxy-butane sulphonic acid dimethylamide

(2R,3S)-3-[N-(BIS-(1-Naphthylmethyl)acetyl)methionyl] amido-4-cyclohexyl-2-hydroxy-butane sulphonic acid dimethylamide

(2R,3S)-3-[N-(BIS-(1-Naphthylmethyl)acetyl)methion(D,L-S-oxid)yl]amido-4-cyclohexyl-2-hydroxy-butane sulphonic acid dimethylamide

(2R,3S)-3-(N-BOC-Phenylalanyl-norleucyl)amido-4-(1-adamantyl)-2-hydroxy-butane sulphonic acid dimethylamide

(2R,3S)-3-(N-BOC-Phenylalanyl-norleucyl)amido-5,5-dimethyl-2-hydroxy-hexane sulphonic acid dimethylamide

(2R,3S)-3-(N-BOC-Phenylalanyl-norleucyl)amido-4-cyclohexyl-2-hydroxy-butane sulphonic acid pyrrolidinamide

(2R,3S)-3-(N-BOC-Phenylalanyl-norleucyl)amido-4-cyclohexyl-2-hydroxy-butane sulphonic acid piperidinamide

(2R,3S)-3-(N-BOC-Phenylalanyl-norleucyl)amido-4-cyclohexyl-2-hydroxy-butane sulphonic acid piperidinamide

(2R,3S)-3-(N-BOC-Phenylalanyl-norleucyl)amido-4-cyclohexyl-2-hydroxy-butane sulphonic acid-(4-benzyl)piperazinamide

(2R,3S)-3-(N-BOC-Phenylalanyl-norleucyl)amido-4-cyclohexyl-2-hydroxy-butane sulphonic acid piperazinamide

(2R,3S)-3-(N-BOC-Phenylalanyl-norleucyl)amido-4-cyclohexyl-2-hydroxy-butane sulphonic acid-(4-acetyl)piperazinamide

(2R,3S)-3-(N-BOC-Phenylalanyl-norleucyl)amido-4-cyclohexyl-2-hydroxy-butane sulphonic acid-[4-(2,5,8,11-tetraoxadodecanyl)carbonyl]-piperazin-amide

(2R,3S)-3-(N-BOC-Phenylalanyl-norleucyl)amido-4-cyclohexyl-2-hydroxy-butane sulphonic acid-4-methyl)piperazinamide

(2R,3S)-3-(N-BOC-Phenylalanyl-norleucyl)amido-4-cyclohexyl-2-hydroxy-butane sulphonic acid-morpholinamide

(2R,3S)-3-(N-BOC-Phenylalanyl-histidyl)amido-4-cyclohexyl-2-hydroxy-butane sulphonic acid-piperidinamide

(2R,3S)-3-(N-BOC-Phenylalanyl-norleucyl)amido-2-hydroxy-5-methyl-mercapto-pentane sulphonic acid dimethylamide

(2R,3S)-3-(N-BOC-Phenylalanyl-norleucyl)amido-2-hydroxy-5-methyl-sulfinyl-pentane sulphonic acid dimethylamide

(2R,3R)-3-(N-BOC-Phenylalanyl-norleucyl)amido-2-hydroxy-4-benzyl-mercapto-butane sulphonic acid dimethylamide

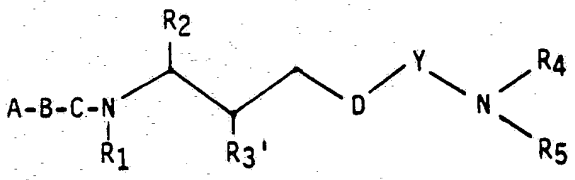
(2R,3R)-3-(N-BOC-Phenylalanyl-norleucyl)amido-2-hydroxy-4-mercapto butane sulphonic acid dimethylamide

(2R,3R)-3-(N-BOC-Phenylalanyl-norleucyl)amido-2-hydroxy-4-ethyl-mercapto-butane sulphonic acid dimethylamide

(2R,3S)-3-[N-(2,3,4,6-Tetra-O-acetylß-D-glucosyl-1-O)-isobutyryl-phenylalanyl-norleucyl]amido-4-cyclohexyl-2-hydroxy-butane sulphonic acid dimethylamide

(2R,3S)-3-[N-(β--D-Glucosyl-1-O)-isobutyryl-phenylalanyl-norleucyl]amido-4-cyclohexyl-2-hydroxy-butane sulphonic acid dimethylamide

5. Process for the preparation of compounds of Formula I according to the preceding claims characterized in that



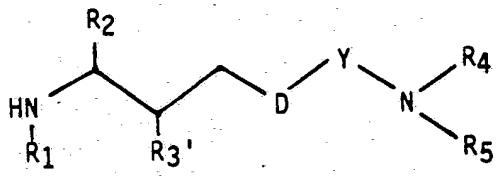
Ia

wherein A, B, C, D, Y, R_1, R_2, R_4 and R_5 are defined as above and R_3' is hydrogen, hydroxyl or a radical of formula $-OCOR_2$.

wherein R_2 is defined as above, may be obtained by reacting compounds of formula II,

A-B-C-OH II

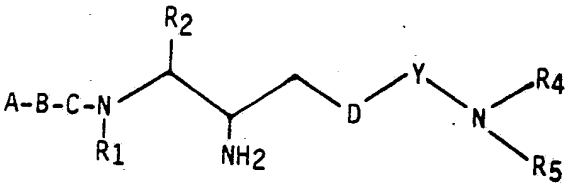
wherein A, B and C are defined as above,
with compounds of formula III



III

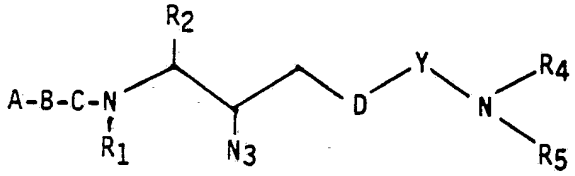
wherein R_1, R_2, R_3', R_4, R_5, Y and D are defined as above,

b) Compounds of formula Ib



Ib

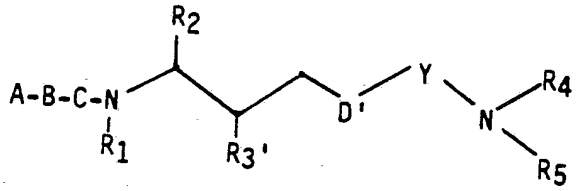
wherein A, B, C, D, Y, R_1, R_2, R_4 and R_5 are defined as above, are obtained by reducing compounds of formula IV



IV

wherein A, B, C, D, Y, R_1, R_2, R_4 and R_5 are defined as above and

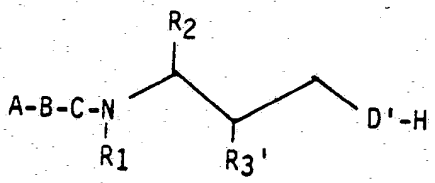
c) Compounds of formula Ic



Ic

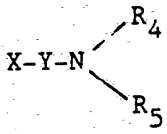
wherein A, B, C, Y, R_1, R_2, R_3', R_4 and R_5 are defined as above, and D' denotes -O- or $-\underset{\underset{R_1}{|}}{N}-$,

wherein R_1 is defined as above
are obtained by reacting compounds of formula V



V

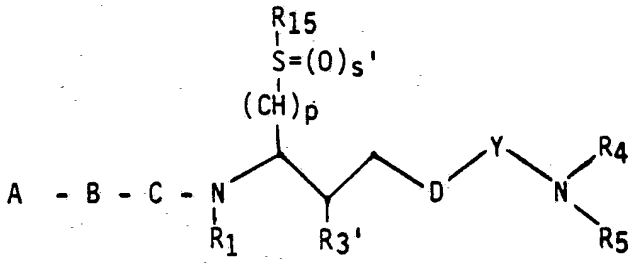
wherein A, B, C, D', R_1, R_2 and R_3' are defined as above with a compound of formula VI



VI

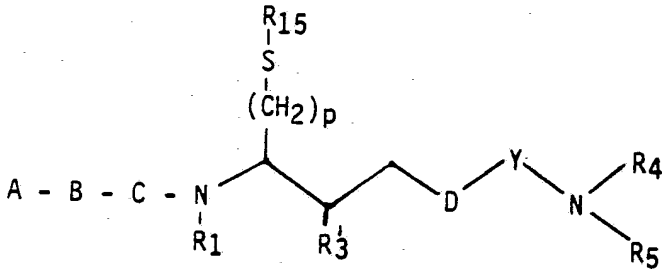
wherein Y, R_4 and R_5 are defined as above, and X signifies halogen, especially chlorine.

d) Compounds of formula Id



Id

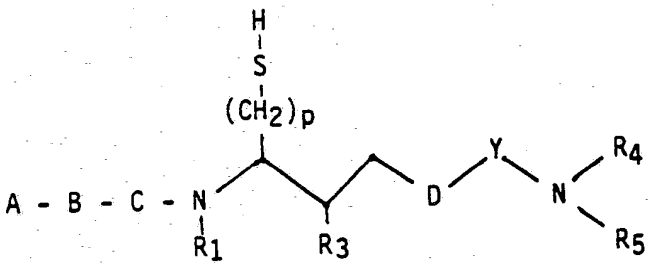
wherein A, B, C, D, Y, R_1, R_3', R_4, R_5, R_{15} and p are defined as above and s' stands for 1 are obtained by oxidation of compounds of formula Ie



Ie

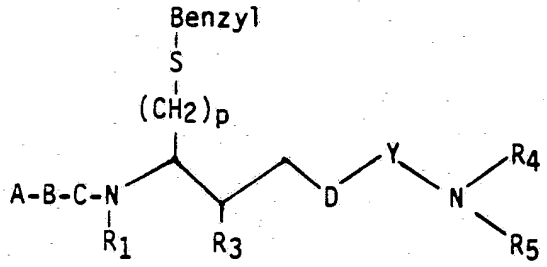
wherein A, B, C, D, Y, R_1, R_3', R_5, R_{15} and p are defined above.

e) Compounds of formula If



If

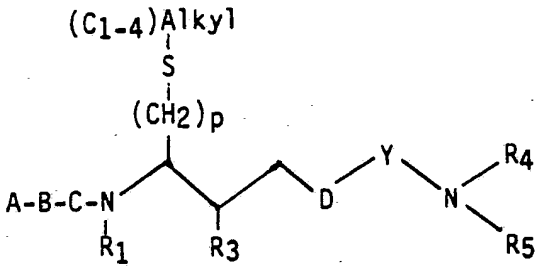
wherein A, B, C, D, Y, R_1, R_3, R_4, R_5 and p are defined above are obtained by splitting off the benzyl group of compounds of formula Ig



Ig

wherein A, B, C, D, Y, R_1, R_3, R_4, R_5 and p are defined above,

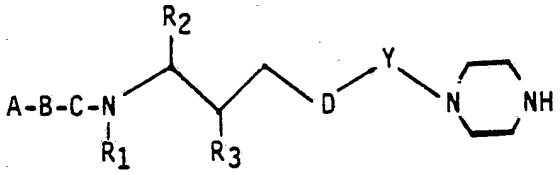
f) Compounds of formula Ih



Ih

wherein A, B, C, D, Y, R_1, R_3, R_4, R_5 and p are defined above are obtained by introducing an alkylgroup in compounds of formula If as defined above.

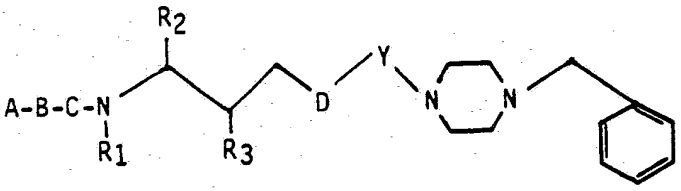
g) Compounds of formula Ii



Ii

wherein A, B, C, D, Y, R_1, R_2 and R_3 are defined above are

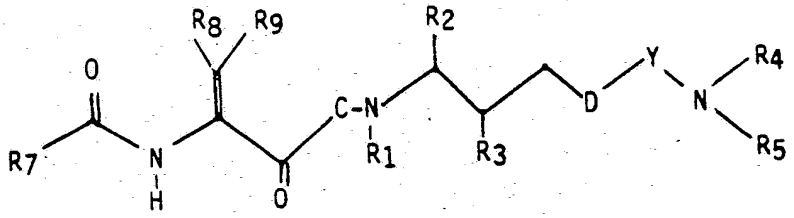
obtained by catalytically splitting off the benzyl group out of compounds of formula Ij



Ij

wherein A, B, C, D, Y, R_1, R_2 and R_3 are defined above.

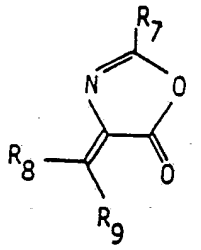
h) Compounds of formula Ik



Ik

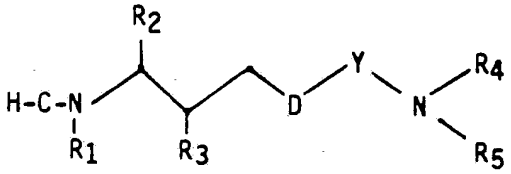
wherein C, D, Y, R_1 to R_5 and R_7 to R_9 are defined as above

are obtained by reacting compounds of formula



IX

wherein R_7, R_8 and R_9 are defined as above with compounds of formula X



X

wherein C, D, Y, R_1 to R_5 are defined as above and obtained precursors of compounds of formula I are optionally transformed in compounds of formula I.

6. Pharmaceutical composition containing compounds of anyone of claims 1 to 4 in pharmaceutically acceptable form in association with a pharmaceutical carrier or diluent.

7. Use of the pharmaceutical composition according to claim 6 for the preparation of medicaments for the treatment of hypertension and congestive heart failure.

8. A method of preventing or treating hypertension or congestive heart failure which comprises administering to an animal in need of such treatment a therapeutically effective amount of a compound of claim 1.

9. A compound of anyones of claims 1 to 4 for use as a pharmaceutical.

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